

## Recent Advances in Essential Tremor

Goksemin A\*

Department of Neurology, Pamukkale University, School of Medicine, Denizli, Turkey

### 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 year's 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 LINGO 1 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/electrophysiological entity. It is the result of pacemaker 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

\*Corresponding author: Goksemin Acar, Department of Neurology, Pamukkale University, School of Medicine, Denizli, Turkey, Tel: 905323817578; E-mail: [goksemind@yahoo.com](mailto:goksemind@yahoo.com)

Received March 03, 2016; Accepted May 20, 2016; Published May 27, 2016

Citation: Goksemin A (2016) Recent Advances in Essential Tremor. J Mult Scler (Foster City) 3:176. doi:10.4172/2376-0389.1000176

Copyright: © 2016 Goksemin A. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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

1. Hardesty DE, Maraganore DM, Matsumoto JY, Louis ED (2004) Increased risk of head tremor in women with essential tremor: longitudinal data from the Rochester Epidemiology Project. *Mov Disord* 19: 529-533.
2. Louis ED, Rios E, Applegate LM, Hernandez NC, Andrews HF (2006) Jaw tremor: prevalence and clinical correlates in three essential tremor case samples. *Mov Disord* 21: 1872-1878.
3. Louis ED, Galecki M, Rao AK (2013) Four Essential Tremor Cases with Moderately Impaired Gait: How Impaired can Gait be in this Disease? *Tremor Other Hyperkinet Mov (N Y)* 3.
4. Gitchel GT, Wetzel PA, Baron MS (2013) Slowed saccades and increased square wave jerks in essential tremor. *Tremor Other Hyperkinet Mov (N Y)* 3.
5. Kronenburger M, Konczak J, Ziegler W, Buderath P, Frank B, et al. (2009) Balance and motor speech impairment in essential tremor. *Cerebellum* 8: 389-398.
6. Louis ED, Ferreira JJ (2010) How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord* 25: 534-541.
7. Romero JP, Benito-León J, Bermejo-Pareja F (2012) The NEDICES Study: Recent Advances in the Understanding of the Epidemiology of Essential Tremor. *Tremor Other Hyperkinet Mov (N. Y)* 1-8.
8. Benito-León J (2014) Essential tremor: a neurodegenerative disease? *Tremor Other Hyperkinet Mov (N. Y)* 4: 252.
9. Louis ED (2009) Essential tremors: a family of neurodegenerative disorders? *Arch Neurol* 66: 1202-1208.
10. Louis ED (2010) Essential tremor: evolving clinicopathological concepts in an era of intensive post-mortem enquiry. *Lancet Neurol* 9: 613-622.
11. Louis ED, Thawani SP, Andrews HF (2009) Prevalence of essential tremor in a multiethnic, community-based study in northern Manhattan, New York, N.Y. *Neuroepidemiology* 32: 208-214.
12. Louis ED (2014) Understanding essential tremor: progress on the biological front. *Curr Neurol Neurosci Rep* 14: 450.
13. Stefansson H, Steinberg S, Petursson H, Gustafsson O, Gudjonsdottir IH, et al. (2009) Variant in the sequence of the LINGO1 gene confers risk of essential tremor. *Nat Genet* 41: 277-279.
14. Vilariño-Güell C, Ross OA, Wider C (2011) *NIH Public Access* 16: 109-111.
15. Romero NB, Lehtokari VL, Quijano-Roy S, Monnier N, Claeys KG, et al. (2009) Core-rod myopathy caused by mutations in the nebulin gene. *Neurology* 73: 1159-1161.
16. Benito-León J, Louis ED, Bermejo-Pareja F; Neurological Disorders in Central Spain Study Group (2009) Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population based study. *J Neurol Neurosurg Psychiatry* 80: 423-425.
17. Shahed J, Jankovic J (2007) Exploring the relationship between essential tremor and Parkinson's disease. *Parkinsonism Relat Disord* 13: 67-76.
18. Deng H, Gu S, Jankovic J (2012) LINGO1 variants in essential tremor and Parkinson's disease. *Acta Neurol Scand* 125: 1-7.
19. de Oliveira RB, Howlett MC, Gravina FS, Imtiaz MS, Callister RJ, et al. (2010) Pacemaker currents in mouse locus coeruleus neurons. *Neuroscience* 170: 166-177.
20. Penington NJ, Tuckwell HC (2012) Properties of I(A) in a neuron of the dorsal raphe nucleus. *Brain Res* 1449: 60-68.

21. Jahnsen H, Llinás R (1984) Ionic basis for the electro-responsiveness and oscillatory properties of guinea-pig thalamic neurones *in vitro*. J Physiol 349: 227-247.
22. Obeso JA (2010) Modeling clinical features of neurodegeneration. Nat Med 16: 1372.
23. Louis ED (2014) Re-thinking the biology of essential tremor: from models to morphology. Parkinsonism Relat Disord 20 Suppl 1: S88-93.
24. Louis ED, Agnew A, Gillman A, Gerbin M, Viner AS (2011) Estimating annual rate of decline: prospective, longitudinal data on arm tremor severity in two groups of essential tremor cases. J Neurol Neurosurg Psychiatry 82: 761-765.
25. Cerasa A, Quattrone A, (2016) Linking Essential Tremor to the cerebellum-neuroimaging evidence. Cerebellum 15: 263-275.
26. Pagan FL, Butman JA, Dambrosia JM, Hallett M (2003) Evaluation of essential tremor with multi-voxel magnetic resonance spectroscopy. Neurology 60: 1344-1347.
27. Thawani SP, Schupf N, Louis ED (2009) Essential tremor is associated with dementia: prospective population-based study in New York. Neurology 73: 621-625.
28. Louis ED, Babij R, Ma K, Cortés E, Vonsattel J-PG (2013) Essential tremor followed by progressive supranuclear palsy: postmortem reports of 11 patients. J Neuropathol Exp Neurol 72: 8-17.
29. Babij R, Lee M, Cortés E, Vonsattel JP, Faust PL, et al. (2013) Purkinje cell axonal anatomy: Quantifying morphometric changes in essential tremor versus control brains. Brain 136: 3051-3061.
30. Fasano A, Deuschl G (2015) Therapeutic advances in tremor. Mov Disord 30: 1557-1565.
31. Zappia M, Albanese A, Bruno E, Colosimo C, Filippini G, et al. (2013) Treatment of essential tremor: a systematic review of evidence and recommendations from the Italian Movement Disorders Association. J Neurol 260: 714-740.
32. Nahab FB, Handforth A, Brown T, Shin C, Quesada A, et al. (2012) Octanoic acid suppresses harmaline-induced tremor in mouse model of essential tremor. Neurotherapeutics 9: 635-638.
33. Shill HA, Bushara KO, Mari Z, Reich MHM (2004) OPen label dose escalation study of oral 1-octanol in patients with essential tremor. Neurology 62: 2320-2322.
34. Bushara KO, Goldstein SR, Grimes GJ Jr, Burstein AH, Hallett M (2004) Pilot trial of 1-octanol in essential tremor. Neurology 62: 122-124.
35. Campbell AM, Glover J, Chiang VLS, Gerrard J, Yu JB (2015) Gamma knife stereotactic radiosurgical thalamotomy for intractable tremor: A systematic review of the literature. Radiother. Oncol 114: 296-301.
36. Elias WJ, Huss D, Voss T (2013) A pilot study of focused ultrasound thalamotomy for essential tremor. N. Engl. J. Med 369:640-8.
37. Lipsman N, Schwartz ML, Huang Y (2013) MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. Lancet Neurol 12: 462-8.
38. Benabid AL, Pollak P, Louveau A, Henry S, De Rougemont J (1987) Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 50: 344-346.
39. Ondo W, Jankovic J, Schwartz K, Almaguer M, Simpson RK (1998) Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson's disease tremor. Neurol 51: 1063-1069.
40. Baizabal-Carvallo JF, Kagnoff MN, Jimenez-Shahed J, Fekete R, Jankovic J (2014) The safety and efficacy of thalamic deep brain stimulation in essential tremor: 10 years and beyond. J Neurol Neurosurg Psychiatry 85: 567-72.
41. Barbe MT, Dembek TA, Becker J, Raethjen J, Hartinger M, et al. (2014) Individualized current-shaping reduces DBS-induced dysarthria in patients with essential tremor. Neurology 82: 614-619.
42. Shih LC, LaFaver K, Lim C, Papavassiliou E, Tarsy D (2013) Loss of benefit in VIM thalamic deep brain stimulation (DBS) for essential tremor (ET): how prevalent is it? Parkinsonism Relat Disord 19: 676-679.
43. Favilla CG, Topiol DD, Zesiewicz TA (2013) Impact of discontinuing tremor suppressing medications following thalamic deep brain stimulation. Parkinsonism Relat Disord 19: 171-175.
44. Chuang WL, Huang YZ, Lu CS, Chen RS (2014) Reduced cortical plasticity and GABAergic modulation in essential tremor. Mov Disord 29: 501-507.
45. Moro E, Schwalb JM, Piboolnurak P, Poon YY, Hamani C, et al. (2011) Unilateral subdural motor cortex stimulation improves essential tremor but not Parkinson's disease. Brain 134: 2096-2105.
46. Johnson MK, Deyo S, Abosch A, Bajwa JA, Johnson MD (2012) Improved spatial targeting with directionally segmented deep brain stimulation leads for treating essential tremor. J Neural Eng 9: 46005.
47. Fasano A, Lozano AM (2015) Deep brain stimulation for movement disorders: 2015 and beyond. Curr Opin Neurol 28: 423-436.
48. Picillo M, Fasano A (2016) Recent advances in Essential Tremor: Surgical treatment. Parkinsonism Relat Disord 22 Suppl 1: S171-175.

Citation: Goksemin A (2016) Recent Advances in Essential Tremor. J Mult Scler (Foster City) 3:176. doi:10.4172/2376-0389.1000176

### OMICS International: Publication Benefits & Features

#### Unique features:

- Increased global visibility of articles through worldwide distribution and indexing
- Showcasing recent research output in a timely and updated manner
- Special issues on the current trends of scientific research

#### Special features:

- 700+ Open Access Journals
- 50,000+ editorial team
- Rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at major indexing services
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.omicsonline.org/submission/>