

Classical essential tremor is defined by persistent, bilateral, mostly symmetric, postural or/and kinetic tremor of the hands and forearms in the absence of other abnormal neurological signs. If essential tremor (ET) is a neurodegenerative disease, by definition, these symptoms are caused by a progressive loss of nervous system structures and functions. To date, there is no clinical, neurophysiological, imaging or pathological evidence proving this hypothesis. Furthermore, reported findings challenge this view and support that tremorgenesis in ET results from pathophysiological mechanisms that lead to increased neuronal oscillations in tremor networks.

In the past decade, several studies have suggested that ET is a widespread disease possibly affecting cognition, mortality, personality, hearing, and olfaction. The reported findings indicate small, inconsistent, and clinically not significant changes. The first results reporting neuropsychological deficits in ET patients were based on non-controlled small sample studies. More recent data suggesting increased frequency of dementia in late onset ET and increased risk for cognitive decline in ET come from large epidemiologic, prospective studies of elderly cohorts with methodological and statistical caveats: about a third of the participants were lost to follow up, some data came from retrospectively reviewed medical records, there were evident sampling biases and statistical analysis did not control confounders such as anxiety and other psychiatric comorbidities; liver and lung disease, or type I errors. Regarding mortality and ET, contradictory results have described increased longevity as well as decreased life expectancy in ET patients. The reported data proposing increased prevalence of mood disorders in ET does not discriminate between cause and effect of chronic disease and disability. Studies regarding possible disturbance of olfaction and hearing are based on small samples and are inconsistent.

Other epidemiology studies have attempted to link Parkinson's Disease and ET, but again, data come from studies in elderly populations with few incident cases. Furthermore, in the largest neuropathological study to date, 24% of patients were found to have Lewy body pathology, in line with the reported 20-30% of incidental Lewy bodies found in asymptomatic elderly people. A

subsequent large study including 24 ET cases did not report an increased incidence of Lewy bodies with respect to controls.

Microscopic cerebellar changes with no evidence of gliosis but significantly increased numbers of axonal torpedoes and reduction of Purkinje cells compared to controls have been reported in ET patients. Torpedoes are a nonspecific sign of Purkinje axonal damage and can be found in normal and pathological conditions in animals and man. Although Purkinje cell loss is an established marker of cerebellar degeneration, ET cases showed a mean reduction of 25% in non-randomized cell counts and this discrete decrease was not correlated with tremor severity or cerebellar signs. Additionally most clinical and histopathological findings come from very elderly patients and therefore must be interpreted cautiously and incidental age-associated pathology, including cerebellar degeneration, must be considered.

The neurodegenerative hypothesis does not explain the early onset and clinically slow progression of ET, which consists of tremor, with minor cerebellar symptoms in some patients and no evident involvement of other brain structures. There is clinical and electrophysiological evidence of cerebellar clinical manifestations in some ET patients. However, reversibility of these symptoms and signs by ethanol or thalamic deep brain stimulation challenges their neurodegenerative origin. Multiple neuroimaging studies using voxel-based morphometry with high-resolution T1-weighted MRI and diffusion weighted MRI also argue against gross structural abnormalities in ET. Furthermore, functional neuroimaging studies in ET show cerebellar hypermetabolism which is hard to reconcile with the idea of cerebellar neurodegeneration.

An alternative hypothesis to ET tremorgenesis is based on inherent neural instability that can lead to generation of central oscillating pacemakers. Through their tight interconnections within motor system networks, these oscillators can become entrained and couple their firing patterns, thus resulting in visible and pathologic tremors. This view allows for different causes leading to changes in motor neuron excitability and thus can account

for the heterogeneity of ET manifestations and therapeutic response. It does not require structural changes in the anatomical organization or connectivity of the cerebello-thalamo-corticocerebellar loops, nor does it exclude structural damage.

Therefore, alterations in neurotransmitters, cation currents, second messengers or receptors can lead to tremors, as postulated in the gly9 susceptibility variant of the DRD3 gene mutation linked to some ET families or GABA mutant mice models. On the other hand, the proposed reduction of cerebellar Purkinje cells or recently discovered LINGO1 gene mutation suggesting axonal changes in some ET patients might affect membrane thresholds and increase the excitability of premotor neurons leading to tremor appearance.

In conclusion, additional prospective studies including young patients and appropriate testing are needed to confirm the existence of non-motor symptoms in ET. Current clinical, neuroimaging, genetic and neuropathological data indicate that ET is a syndrome rather than a unique disease and therefore may be caused by multiple conditions leading to a dynamic oscillatory disturbance of cerebello-thalamic-basal ganglia-cortical networks.