Essential Tremor

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Abstract

Essential tremor is the most frequent movement disorder with a prevalence of 2-4%. It is underdiagnosed and may be misdiagnosed as Parkinsonian tremor, physiologic or cerebellar tremor. The most consistent symptom is an involuntary, rhythmic tremor of the hands or arms, although the tremor can affect any body part. The tremor is mainly manifested during posture maintenance and action, but may occur during targeted movements and, rarely, at rest. Tremor is the major complaint of the patients, although a mild gait disturbance may also occur. Cognition, sensory system and life expectancy are not affected by this chronic disease. The age of onset vary widely, but two onset peaks are described around the 2nd and 6th decade. In ~70% of patients, the tremor is temporarily improving after ingestion of small amounts of alcohol. A positive family history can be found in ~ 80% of the patients, suggesting a hereditary cause. The causative genes have not yet been detected, but two chromosomal loci have been linked to the disease. Treatment options include Propranolol, Primidone, Gabapentine, Clonazepam and deep brain stimulation.

Keywords
Essential tremor, familial tremor, hereditary tremor

Disease names / synonyms
- Essential tremor (ET)
- Hereditary tremor
- Familial tremor
- Benign essential tremor

Definition/diagnostic criteria
ET is defined as a bilateral postural and/or action tremor of the hands or the head. The diagnosis of definite ET requires a slowly progressive condition with a duration of at least 3 years. At present, the diagnostic criteria are still a matter of debate. The current definition has been published in a consensus statement by the Movement Disorder Society (Deuschl et al., 1998), which distinguishes ‘definite’, ‘probable’ and ‘possible’ ET. Other diagnostic sets are the NIH Collaborative Genetic Criteria from 1996 (Chouinard et al., 1997). For diagnosing ET, one should assess:
- the anatomic distribution of tremor;
- the activation condition of the tremor (rest, posture, intention);
- the tremor amplitude and frequency;
- the muscle contraction pattern as agonist-antagonist interaction;
- the degree of functional disability and handicap;
- the psychosocial problems and the impact on the patient's life;
- the duration of tremor;
- the history of disease progression;
- the family history of tremor;
- the sensitivity of tremor to alcohol;
- the coexistence of other neurological signs or symptoms;
- the current medication and the response to current and previous medications.

Differential diagnosis

Differential diagnoses of essential tremor are other movement disorders, such as Parkinsonian tremor, dystonic tremor, cerebellar tremor, Holmes tremor, psychogenic tremor and the large group of symptomatic tremors. This group includes drug-induced, toxic and metabolic tremors, tremor syndromes in polyneuropathy or after severe head trauma or stroke. Furthermore, some other movement disorders may be misinterpreted as tremor, such as myoclonus, asterixis, clonus, rhythmic dyskinesias and stereotypies or epilepsy partialis continua.

With regard to the differential diagnosis of Parkinson's disease (PD), it is important to know that Froment's sign and possibly even cogwheeling may be present in ET, but not rigidity or akinesia. In addition, unilateral tremor and leg tremor are manifested in PD but not in ET.

Etiology

Epidemiologic studies suggest a genetic cause of ET (Larsen and Sjögren, 1960). Inheritance seems to follow an autosomal dominant pattern in most familial cases. Penetrance is nearly complete by the age of 65 to 70 years. Sporadic cases have been also described. Positive family history reported by the patients varies from 25% (Louis et al., 2001) to 60% (Busenbark et al., 1996) in different studies. This variability may be explained by different aspects: 1. the complete penetrance of the disease at old age may lead to a misclassification of patients who died at younger age as tremor negative; 2. the recognition of tremor depends on the individuals perception and varies widely, especially for milder tremor forms; 3. the contact with other family members may be limited; 4. patients with tremor try to hide it and thereby family members may be not aware of other affected members.

A recent twin study has confirmed the importance of genetic factors in ET, suggesting that environmental causes play only a limited role in the disease's etiology (Lorenz et al. 2004, in press).

Pathophysiology

ET is believed to be due to an abnormality within the Guillain-Mollaret triangle (rubral nucleus, olivary nucleus and cerebellum). The cerebellum seems to be crucially involved into the pathogenesis of ET, since a lesion of the cerebellum can completely stop ET ipsilaterally. Recent studies have confirmed that cerebellar functions are slightly affected in ET (Deuschl and Elble, 2000). Recent imaging studies with spectroscopy of the cerebellum have shown abnormalities compatible with a cell damage in cerebellar neurones (Louis et al., 2002; Pagan et al., 2003).

Clinical description

ET is a slowly progressive, chronic condition characterized by involuntary, rhythmic activity of a body part. The symptoms may begin at any age, but two onset peaks are described around the second and the sixth decade (Bain et al., 1994). ET may occur in every body part. However, bilateral and symmetrical hand and arm tremor is most common and occurs during posture maintenance and action. Previous studies have shown that 90 to 100% of patients have hand tremor. Head tremor is found in 40-60% of patients and may occur rarely without hand tremor. Voice tremor occurs in approximately 30% of patients, followed by leg tremor (15 - 45%) and even less frequently, chin, tongue and trunk tremor (Lou and Jankovic, 1991). In severely affected patients, rest tremor (Cohen et al., 2003), as well as cerebellar signs, such as intention tremor (Deuschl et al., 2000) and impairment of tandem gait (Stolze et al., 2001) may be seen. The tremor frequency varies from 4-12 Hz.

Diagnostic methods

ET is a clinical diagnosis, and there is no definitive test available. However, it is possible to use electrophysiologic techniques like accelerometry or electromyogram (EMG) to measure the tremor frequency and amplitude and to show the muscle contraction pattern. For tremor assessment, tremor classification scales are used (e.g., Fahn’s or Bain’s tremor scale). A further important point is the assessment of the tremor’s impact on the patient, using disability and handicap scales or questionnaires on quality of life.
Epidemiology
ET prevalence estimates vary widely in different studies, from 0.008 to 22% (a 2750-fold difference). However, this wide range of prevalence data is reduced between 0.41 to 3.92% when considering only studies which provided accurate diagnostic criteria and age-stratification. In the age group above 60 years the prevalence of ET is 1.3 to 5.05% (Louis and Ottman, 1996). Incidence has not been widely assessed. A retrospective 45 year-study of ET in Rochester revealed an age-adjusted incidence of 17.5/100,000/year.

Genetic counseling
To date, two chromosomal loci have been linked to ET: they map to chromosomes 3q13 (ETM 1) (Gulcher et al., 1997) and 2p22-25 (ETM 2), respectively (Higgins et al., 1998). An association study on 45 unrelated patients with a family history of ET and 70 controls, provided evidence that the ETM2 locus may play a role in a substantial proportion of patients with familial ET (Higgins et al., 2003).

Management
Drug therapy in ET is a symptomatic therapy and hitherto neither a curative nor a neuroprotective therapy has yet been discovered (Wasielewski et al., 1998).

The first-line treatments are the Propranolol and Primidone:
The β-blocker Propranolol should be tried first in the younger patients without contraindications (asthma, certain heart problems (e.g. AV block), diabetes mellitus, pulmonary diseases, peripheral vascular disease). The initial dosage is 3x10mg and can gradually be increased. The maximal daily dosage is 240-320 mg. Long-acting preparations can be used. Successful therapeutic effects are most often obtained with dosages between 80-160 mg/d. Propranolol can be used as intermittent therapy for stressful situations. The β-blocker should be discontinued gradually. Approximately 50 to 70% of patients obtain some symptomatic relief by this therapy, even though a complete suppression of the tremor is rare. Side effects of this therapy are hypotension, dizziness, fatigue, nausea, changes in blood sugar levels and sexual difficulties, mainly in men.

Primidone is the first-line treatment in older patients and patients with contraindications for β-blockers. The starting dosage should be as low as 30 to 62.5 mg and the dose should be given in the late evening to avoid sleepiness. An acute adverse reaction including dizziness, nausea and vomiting can occur, is dose dependent and mostly ceases after induction of liver enzymes. Afterwards the dose should be raised very slowly as needed. The maximal dosage is 750 mg/d. However, often a dosage between 125 and 375 mg/d has already a satisfactory effect. Primidone should be discontinued gradually. Many patients respond positively to primidone, but often a decreasing effect over time can be obtained. Side effects are also more frequent under primidone therapy in comparison to propranolol. These may be sleepiness, dizziness, nausea, ataxia and confusion.

The third step in ET drug therapy should consist of a combination of Propranolol and Primidone.

Second-line drug therapies for the treatment of ET include Gabapentin, Topiramate, Clozapine, long acting benzodiazepines, such as Clonazepam and local injections of botulinum toxin-therapy.

Gabapentin has been associated with a positive therapeutic effect in open studies as well as in two double-blind, placebo-controlled trials (Gironell et al., 1999; Ondo et al., 2000). Another double-blind, placebo-controlled trial reported no significant therapeutic effect of Gabapentin (Pahwa et al., 1998). Gabapentin should be started at doses of 3x100 mg/d. Maximal dose is 2400 mg/d. A therapeutic effect can often be seen with a dosage of 1800 to 2400 mg/d.

Topiramate has shown a positive effect on ET in one double-blind, placebo-controlled trial, in which 24 patients were treated in a cross-over design (Connor, 2002). Dosage should be started at 25 mg/d, and maximal dose is 400 mg/d.

Clozapine has shown a therapeutic effect in a small double-blind, placebo-controlled cross-over trial. This finding has not yet been replicated and does not fit with the personal experience of the authors. Additionally, possible agranulocytosis is a substantial risk.

Classical sedatives, such as long-acting benzodiazepines may have a positive effect on ET as well.

Local injections of botulinum toxin-therapy may have a benefit in selected patients with ET (Brin et al., 2001). Most often this kind of therapy is used in patients with essential head tremor.

Deep brain stimulation is another option in essential tremor therapy. It has shown a positive effect in several studies (Koller et al., 2001; Limousin et al., 1999; Rehncrona et al., 2003). Target area of the electrodes is the nucleus ventralis intermedius (VIM) of the thalamus. Patients should be selected for this therapy on the basis of strict criteria: no satisfactory effect under drug therapy and severe suffering from the disease.
Unresolved questions
Many aspects of ET involving clinical features, pathophysiology, genetic causes and treatment warrant further research, which would specifically gain from hypothesis-driven studies.

References