Baylor College of Medicine
DEPARTMENT OF NEUROLOGY

Parkinson's Disease Center
and Movement Disorders Clinic
7200 Cambridge Street, 9th Floor, Suite 9A ▪ Houston, Texas 77030
713-798-2273 phone ▪ pdcmdc@bcm.edu ▪ www.jankovic.org

Essential Tremor

Tremor, an oscillatory movement produced by rhythmic contractions of muscles, is the most common form of involuntary movement, but only a small fraction of those who shake seek medical attention. Essential tremor (ET) is the most common form of tremor, affecting about 5 percent of people over the age 60 years. Although ET is more common in the elderly and is often wrongly labeled as "senile tremor" it may start at any age. Studies have shown that there is a bimodal distribution of age at onset with peaks in the 2nd and 6th decades. In contrast to rest tremor, which is most frequently secondary to Parkinson's disease, ET is typically an action-postural tremor. Patients usually first become aware of the tremor when they are holding newspapers or utensils or when reaching for objects. ET can also affect the neck muscles and produce either "yes-yes" or "no-no" oscillation of the head, and the vocal cords, noted as a tremulous voice while singing or talking. A review of the clinical features in 350 consecutive patients diagnosed with ET referred to the Movement Disorders Clinic at Baylor College of Medicine has shown that hands are involved in 90 percent of all ET patients, head in 41 percent, voice in 17 percent, and legs in 14 percent. Stress, overactive thyroid and certain drugs can exacerbate the tremor. Despite the frequently used prefix "benign" ET can produce significant physical and psychosocial disability. In addition to social embarrassment, ET can interfere with writing, eating, speaking, singing and various other activities of daily living. Although the tremor frequency tends to decrease with age, the amplitude usually increases and the tremor may become more and more troublesome.

In some cases, tremors occur only during a particular task, such as writing, or while holding limbs in certain position such as when bringing a glass to the mouth. These task-, and position-specific tremors are considered variants of ET, but in some cases the clinical features overlap with another movement disorder, called dystonia. Dystonia is manifested an involuntary sustained contraction of muscles

producing abnormal movements or postures. Examples of dystonia include writer's cramp, torticollis or wry neck (cervical dystonia), and involuntary eye closure (blepharospasm). In some patients, dystonia produces rhythmical movements resembling ET, but in contrast to ET, dystonic tremor is more irregular and is more influenced by the position of the affected body part. Some studies have suggested that there is an association between ET and dystonia, and between ET and Parkinson's disease. This is supported by the reports of well-studied families in which some members have typical ET, while others have dystonia, parkinsonism or a combination of all three disorders. Furthermore, some patients start with typical ET and several years or decades later develop associated parkinsonism or dystonia, or both. Although it should not be difficult to differentiate tremor of ET and tremor typically seen in patients with PD, the occasional co-existence of the two disorders in the same individual may present a diagnostic challenge. In addition to dystonia and parkinsonism, patients with ET seem to have a higher frequency of deafness, hereditary neuropathy, cognitive problems, mild incoordination and loss of balance. Orthostatic tremor is a fast tremor, involving mainly legs and trunk. It is present chiefly on standing and may be associated with a feeling of unsteadiness and calf cramps, relieved by sitting or by assuming a supine position.

Causes

Frequently misdiagnosed as a stress-related condition or a natural consequence of aging, ET is actually a manifestation of a genetic neurological disorder. Family history of tremor is present in the vast majority of patients. Despite the overwhelming evidence that ET is a genetic disorder, the gene for ET have not yet been fully identified. A lot of genes were initially implicated in ET, such as *LINGO1, FUS*, and *TENM4*. The difficulty on finding one gene despite multiple studies generated the idea that ET is likely the result of the effect of multiple genes in combination with environmental factors. Beta-alkaloids (harmine and harmane) and lead were implicated in ET.

Currently, ET is considered the result of a dysfunction in the network that coordinates movements, which involves the cortex and deeper areas of the brain

such as the thalamus, cerebellum, and olivary nucleus. Loss and swelling of specialized cells called Purkinje cells in the cerebellum and changes in the production of GABA were reported, but no clear mechanism was defined.

Treatments

The treatment of tremor depends largely on its severity; many patients require nothing more than simple reassurance. Most patients who are referred to a neurologist, however, have troublesome tremors that require pharmacologic or surgical treatments. The large amplitude and slow frequency postural tremors usually do not respond well to pharmacologic therapy.

Since alcohol reduces the amplitude of ET in about 2/3 of patients, some patients use it regularly for its "calming" effect and some use it before an important engagement where the presence of tremor could be a source of embarrassment. Regular use of alcohol to treat ET is not recommended.

Propranolol and primidone are the most effective medications to treat ET. Propranolol (Inderal) is a beta-adrenergic blocker, and it has immediate-release and extended-release formulations. It is usually well tolerated, but patients can experience side effects, such as fatigability, sedation, depression and erectile dysfunction. Propranolol is contraindicated in the presence of asthma and insulin-dependent diabetes. The anti-tremor effect of primidone (Mysoline) has been confirmed by several clinical trials. By starting primidone at a very low dose, the occasional side effects (nausea, vomiting, sedation, confusion and loss of balance) can be prevented. A combination of the two drugs, propranolol and primidone, may be more efficacious than either drug alone.

In addition to propranolol and primidone, other beta blockers such as pindolol and nadolol, benzodiazepine drugs, such as lorazepam (Ativan) and clonazepam (Klonopin) also may also improve ET and its variants. Gabapentin (Neurontin), topiramate (Topamax), and pregabalin (Lyrica), drugs approved for the treatment of epilepsy, may be also useful in the treatment of tremors. Gabapentin, levodopa, primidone, clonazepam, and phenobarbital may be useful in patients with orthostatic tremor, a possible variant of ET. Patients with head tremor do not

usually respond to medications, but can be effectively treated with botulinum toxin (BTX) injections into the neck muscles. BTX is also effective in the treatment of hand tremor. Usually well tolerated, BTX can produce transient weakness of the injected muscles.

Neurosurgical treatments, such as deep brain stimulation (DBS), are generally reserved for patients whose tremors continue to interfere with work or activities of daily living despite optimal medical therapy. DBS involves an incision in the scalp and drilling a hole in the skull. The surgeon then uses a "probe," a wire electrode, and advances the electrode into the portion of the brain that is thought to be functioning abnormally. The DBS lead, which actually contains four electrodes, is surgically inserted into the desired target and fixed to the skull with a ring and cap. An extension wire passes from the scalp area under the skin to the chest and is connected to a totally implantable pulse generator (IPG), a pacemaker-like device, which can deliver pulses with a variety of parameters, modes, and polarities into the target brain area. The IPG is placed under the skin in the upper chest area near the collar bone. The patient can activate or deactivate the DBS system by placing a hand-held device over the chest area that contains the IPG. The major advantage of DBS over the traditional ablative procedures is that the stimulating electrodes and parameters (frequency of stimulation, pulse width, and voltage) can be adjusted to the needs of the individual patients. Potential risks, such as hemorrhage, stroke or infection, are rare, but should be considered when making a final decision about this treatment option. Side effects, if they occur, are usually reversible, but may include weakness, speech and swallowing difficulties, and abnormal sensations. The benefits of DBS persist even after more than 10 years of treatment. Another technique recently described to treat medically-refractory ET is the focused ultrasound thalamotomy. In this procedure, the patient lies down in a MRI machine with a head frame and an ultrasound coupled with the MRI will cause a lesion in the brain. This technique does not involve drilling a hole in the skull as the ultrasound waves are able to cross the bone. The side effects reported were numbness in the face and hand, balance problems and weakness.

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Support Group
International Essential Tremor Foundation
PO Box 14005
Lenexa, KS 66285-4005
Phone: (913) 341-3880
Toll free: (888) 387-3667
Fax: (913) 341-1296
Email: info@essentialtremor.org