An Update on Essential Tremor

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Essential tremor is a well-defined syndrome of postural and kinetic tremor in a characteristic distribution. In some patients, impaired tandem walking, intention tremor, and rest tremor are also seen. An increasing body of clinical, neuropathological, and epidemiologic evidence suggests that essential tremor is a heterogeneous disorder. The evidence is discussed in this update. Recent advances in the treatment of this condition are also reviewed.

Introduction

Essential tremor (ET) is the most common form of abnormal tremor in adults. In this update, we review the clinical characteristics, nonmotor signs, pathophysiology, and treatment of ET. The controversies surrounding this disorder are emphasized, with focus on reports published during the past 4 years.

Clinical Characteristics

Classic ET affects the upper limbs in at least 95% of patients. Experts disagree as to whether patients with isolated head tremor should be included in studies of "definite" or "classic" ET [1]. Some investigators include isolated head tremor if there is no evidence of dystonia or abnormal posturing of the head and neck. However, cervical dystonia is a common disorder, and tremor is common in patients with cervical dystonia. Patients with cervical and cranial dystonia often have tremor in the hands [1], and dystonia is easily overlooked when it is predominantly tremulous or when it begins with pure tremor. Therefore, the current trend is to exclude isolated head tremor from classic or definite ET. Similarly, other task-specific and focal tremors, such as isolated chin tremor, writing tremor, and vocal tremor, are usually viewed as conditions separate from classic ET.

Nevertheless, it is common for ET to affect the head (≥ 34%), face/jaw (≈ 7%), voice (≥ 12%), tongue (≈ 30%), trunk (≈ 5%), and lower limbs (≈ 30%) [2]. In all affected body parts, ET classically occurs in posture and movement. Patients with advanced ET often exhibit crescendo tremor as the hand approaches its target, and this intention tremor is indistinguishable from the intention tremor caused by lesions in the deep cerebellar nuclei and their outflow tract to the contralateral ventrolateral thalamus [3]. In addition, some ET patients have impaired tandem walking [4]. These signs are observable at the bedside and are consistent with the belief that the cerebellum is involved in tremorogenesis.

Rest tremor may develop in patients with advanced ET [5,6], but in many instances "rest tremor" is actually a postural tremor that is caused by incomplete muscle relaxation. This common error can be avoided by examining patients in recumbent and seated positions with complete body support. Monosymptomatic rest tremor is nearly always a sign of Parkinson's disease or some other form of parkinsonism [7]. Rest tremor in ET never occurs in the absence of prominent postural and kinetic tremor [2] and may be the initial sign of coexistent PD [5]. Cogwheeling during passive limb manipulation is simply palpable tremor, and cogwheeling without rigidity is common in the affected limbs of ET patients and should not be regarded as a sign of Parkinson's disease [1].

Nonmotor Signs

ET has been traditionally viewed as a neurologic condition with no abnormal signs other than tremor, and additional neurologic signs or symptoms are regarded as red flags that some other disorder is present, either in isolation or in combination with ET [8]. However, a host of recent studies have purported to show nonmotor deficits in patients with ET.

Cognitive deficits have been reported by several investigative groups and summarized by Higginson and coworkers [9]. All of the studies failed to control for one or more of the following important variables: depression, anxiety, education, comorbidities, medications, small sample size, multiple comparisons (statistical tests), and sampling bias. Nevertheless, these studies have been somewhat consistent in their demonstration of below-average performance in frontal cognitive functions. All reported cognitive deficits have been asymptomatic group differences in cohorts of ET patients compared with healthy controls, and there is no evidence that symptomatic cognitive impairment is caused by ET.

A large epidemiologic study in Spain recently found that both the prevalence and incidence of dementia were increased (absolute increase ≈ 4%) in patients with late-onset (age > 65 years) ET [10,11]. This surprising observation supports the notion that many cases of late-onset ET have a different pathophysiology than early onset ET. Furthermore, Alzheimer's disease, Lewy body disease, and the tauopathies are common in the elderly and could affect motor pathways in ways that are tremorogenic. The clinical characteristics of ET in the upper limbs are nonspecific, and identical action tremor can be the sole presenting symptom in other tremorogenic diseases, such as Parkinson's disease and dystonia [8].

Studies of personality in ET have revealed increased anxiety and harm avoidance [12,13]. These personality traits are possibly confounders in the published reports of cognitive impairment.

Louis and coworkers [14] found mild subclinical olfactory impairment in a group of ET patients, but this has not been found in other studies [15]. There is no evidence of severe or symptomatic olfactory impairment in ET.

Ondo and coworkers [16] found increased hearing disability in ET patients compared with controls and patients with Parkinson's disease, and this impairment was correlated with tremor severity, older age, and male sex. Audiologic testing revealed greater age-dependent high-frequency hearing loss than reported in the literature. In a population-based epidemiologic study, Benito-Leon and coworkers [17] found that 96 of 248 patients (38.7%) with ET reported hearing loss, versus 1371 of 4669 controls (29.4%). Audiologic testing was not done. Additional prospective studies are needed with adequate controls for age, medications, occupation (noise exposure), and medical comorbidities.

Pathophysiology

The fundamental abnormality in ET is abnormal rhythmic motor unit entrainment at frequencies of 4 to 12 Hz. This motor unit activity reflects similar neuronal oscillation and entrainment throughout central motor pathways. The cause of this neuronal activity is the critical question in ET research.

About 50% of patients have a family history of ET [2], and many cases are inherited in a mendelian-dominant fashion with a high genetic penetrance by age 65 [18]. Linkage studies of many large families have produced several candidate loci, but a specific gene has not been found [19••]. The reasons for this disappointing progress are uncertain. ET is very common and may have multiple genetic and nongenetic etiologies. Consequently, multiple phenocopies could occur in large families. Polygenic inheritance of multiple common ET alleles is also possible and could cause an apparent autosomal dominant pattern of inheritance. If so, genomewide association studies will be necessary to find the responsible genes. Recently, such a study found that a variant in the *LINGO1* gene confers increased risk of ET [20]. More studies of this type are needed.

Lorenz and colleagues [18] found nearly complete concordance for classic ET in elderly monozygotic twins; thus, genetic inheritance may be sufficient for the development of tremor in many families. However, the absence of complete concordance in monozygotic twins suggests that environmental factors also may play a role. In this regard, Louis and coworkers [21] found a small elevation of blood harmane in patients with ET, and the blood concentrations of this substance correlated with a reduction in the ratio of cerebellar *N*-acetyl-L-aspartate to total creatine. Harmane is tremorogenic in laboratory animals and is present in the human diet (in meat). Blood harmane levels are higher in patients with familial ET, which may be an example of interacting genetic and environmental factors [21]. Other environmental factors have not been found, with the possible exception of lead and exposure to agricultural work [22••].

Before 2004, routine postmortem studies revealed no consistent abnormalities in patients with ET [6]. However, subsequent quantitative studies of 33 patients revealed limited brainstem Lewy body formation in 25% and cerebellar Purkinje cell loss, Bergmann gliosis, and axonal torpedoes in 75% [23••]. All 33 patients were older than 70 at the time of death. Shill and coworkers [24] found similar cerebellar pathology in 7 of 24 elderly patients, but the incidence of Lewy bodies was similar to that in controls. Moreover, significant incidental neuropathology was common in the patients and controls. Lewy bodies are found in more than 10% of asymptomatic elderly people and are much more common in patients with cognitive impairment [25,26]. Furthermore, it is conceivable that Purkinje cell loss is caused by tremor, not vice versa, in a manner similar to the cell loss caused by tremorogenic indole alkaloids such as ibogaine and harmaline [27]. Postmortem examinations of younger patients and several affected people in the same family must be studied to exclude the possibility of spurious or coincidental pathology.

Despite the uncertainties regarding neuropathology, many clinical observations suggest that ET emerges from abnormal oscillation within the cerebellothalamocortical pathway [28,29••]. Lesions in the cerebellum and thalamus greatly reduce ET. Tremor-correlated neuronal discharge is routinely recorded from the ventrolateral thalamus (ventralis intermedius) during stereotactic surgery, and electrophysiologic studies have demonstrated enhanced cortical rhythmicity in patients with ET. Contralateral limb tremor is suppressed by ablation and high-frequency stimulation of ventralis intermedius. Positron emission tomography studies have revealed bilaterally increased olivary glucose utilization and bilaterally increased blood flow in the cerebellum, red nucleus, and thalamus. Functional MRI studies have disclosed increased blood flow bilaterally in the cerebellar hemispheres, dentate nucleus, and red nucleus and contralaterally in the globus pallidus, thalamus, and primary sensorimotor cortex. Magnetic resonance spectroscopy revealed reduced ratios of *N*-acetyl-L-aspartate to creatine in the cerebellar cortex, consistent with neuronal loss [23••].

Treatment

Medications

In 2005, the treatment of ET was summarized by a quality standards subcommittee of the American Academy of Neurology [30]. Propranolol and primidone are the only two medications with unequivocal efficacy. However, only 50% of patients with ET benefit from one or both of these medications, and response to one does not predict response to the other. The average reduction in tremor is about 50%, and complete suppression of tremor is rare. The beneficial effect is largely limited to hand tremor.

More recently, a large multicenter placebo-controlled trial of topiramate revealed modest efficacy [31]. A small double-blind controlled trial of pregabalin produced encouraging results that require confirmation in a larger study [32]. Small studies of zonisamide, levetiracetam, gabapentin, amantadine, benzodiazepines, methazolamide, flunarizine, nimodipine, clonidine, low-dose theophylline, clozapine, mirtazapine, and 3,4-diaminopyridine have produced inconclusive or negative results [33].

Botulinum toxin injections into the forearm muscles can produce modest improvement in hand tremor, but finger or wrist weakness is a nearly universal side effect [30,34]. Greater efficacy has been reported occasionally in patients with disabling head tremor and voice tremor, but this experience is largely anecdotal [34].

Because many patients respond dramatically to ethanol, other forms of alcohol have been sought for therapeutic trials. The 8-carbon alcohol octanol suppressed essential hand tremor in a pilot study of ET [35], and sodium oxybate produced substantial improvement in a pilot study of ethanol-responsive patients [36]. Additional studies are needed to demonstrate the tolerability and long-term efficacy of these alcohols, particularly in patients who do not respond to ethanol.

Surgery

Stereotactic surgery is the most effective treatment for ET but is generally reserved for severe drug-resistant tremor [30]. For decades, the thalamic nucleus ventralis intermedius has been the preferred target for thalamotomy and deep brain stimulation (DBS). DBS is the preferred procedure because it produces greater functional improvement with fewer side effects and because bilateral DBS can be performed without disabling dysarthria, dysphagia, and ataxia [30]. Marked suppression of limb tremor is achieved in 70% to 90% of patients [30], and about the same percentage experience reduced voice and head tremor after bilateral surgery [37,38].

Efficacy from DBS is gradually lost in some patients. Suboptimal lead placement, physiologic tolerance, and disease progression are possible explanations for this phenomenon. Most investigators believe that suboptimal lead placement is usually the problem [39,40].

Some patients do not respond well to DBS in ventralis intermedius, and this nucleus may not be the best target for all patients. In 2003, Murata and coworkers [41] reported that DBS in the posteromedial subthalamic area was beneficial in patients with refractory intention tremor involving the proximal muscles of the upper limbs. Since then, other investigators have reported similar results, and some have found that stimulation of the subthalamic area is more effective that direct thalamic stimulation in the treatment of advanced ET [42•,43]. The critical target in this anatomically compact area is unclear but is probably the zona incerta and prelemniscal radiation, which carry cerebellar and somatosensory afferents to the ventrolateral thalamus. Parkinson tremor and ET both respond to subthalamic DBS when they occur in the same patient [44].

The mechanism of DBS is a topic of ongoing investigation. There is increasing evidence that thalamic and subthalamic DBS suppresses tremor by driving motor circuits at high frequencies to reduce tremorogenic neuronal firing [42•]. This hypothesis is consistent with the observations that thalamic and subthalamic stimulation frequencies greater than 60 to 90 Hz suppress tremor while simulation frequencies below 60 Hz are tremorogenic [45]. The optimum frequency of stimulation is about 130 Hz [46]. Higher frequencies provide little or no additional benefit, and they reduce battery life of the stimulator. The frequency, voltage, pulse width, and electrode configuration can be optimized with stimulator programming.

In its 2005 practice parameter, the American Academy of Neurology's quality standards subcommittee concluded that there was insufficient evidence to recommend stereotactic gamma-knife thalamotomy as a safe and effective alternative to DBS. Good to excellent results in about 70% of patients have been reported, but there are still no controlled studies [47]. Furthermore, the response to treatment is delayed, taking 1 to 4 months to a year or more, and there is considerable variability in the size of the lesion produced by a specific dose and area of radiation [47]. Disabling delayed complications have occurred [47]. Because of these problems, advocates of gamma-knife thalamotomy offer this procedure to patients who are considered to be poor candidates for thalamic DBS, such as elderly patients with disabling comorbidities, therapeutic anticoagulation, or coagulopathies. Such patients are uncommon, and few centers have enough experience to be confident in this procedure. Major long-term risks cannot be excluded.

Conclusions

The ET "lumpers" and "splitters" have been debating for years, but frequently the magnitude of disagreement is more apparent than real. On the one hand, ET is a well-defined clinical condition in which the examiner finds postural and kinetic tremor in a characteristic distribution and, in some patients, impaired tandem walking, intention tremor, and rest tremor. We believe there is insufficient evidence to include other neurologic signs in this syndrome, even though tremor resembling ET can occur in other diseases, such as dystonia and Parkinson's

disease. ET is so common that coincidental occurrence with other diseases is commonplace. Attempts to lump ET with other diseases have typically led to erroneous conclusions, even in large families with apparent autosomal dominant inheritance [48].

On the other hand, an increasing body of clinical, neuropathological, and epidemiologic evidence suggests that ET is a heterogeneous disorder [23••]. Postmortem studies have not revealed uniform abnormalities [23••], and some epidemiologic associations in late-onset ET have not been present in early-onset and familial ET [10,11]. Tremorogenic neurologic comorbidities are common in the elderly, and patients with late-onset tremor tend to progress more rapidly [49•]. Thus, substantive differences may exist in the pathophysiology of early-onset and late-onset ET. The electrophysiologic and clinical characteristics of ET are not unique or diagnostic, and there is no diagnostic test for ET. Consequently, caution is necessary when diagnosing this disorder, particularly in sporadic late-onset cases with hand tremor of short duration, focal or task-specific tremor (eg, head, voice, hand), and any sign of parkinsonism or dystonia.

The impact of ET heterogeneity on published treatment trials is unknown. Future trials should address this concern. Fortunately, DBS is very effective in most patients, although the optimum stereotactic target may be the posterior subthalamic area rather than the ventralis intermedius proper, particularly for patients with prominent involvement of proximal muscles and with coexistent Parkinson's disease.

Disclosure

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Dr. Deuschl is a consultant for Medtronic, Teva Pharmaceuticals, and Lundbeck.

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