Practical Approach to Diagnosis and Management of Essential Tremor

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Disclosures

• NONE
Outline

- Diagnostic Criteria
- Clinical Characteristics
- Differential Diagnosis
- Pharmacological Treatment
- Surgical Treatment
- Future Directions
1874, “tremore semplice essenziale” by Pietro Burresi, Professor of Medicine at the University of Siena, Italy

- 18 year-old man with severe action tremor
- Head tremor
- Absence of paralysis or other central nervous system signs

Diagnostic Criteria

Tremor Investigation Group:
- Bilateral postural tremor with or without kinetic tremor
- Can have additional tremor
- Duration longer than five years

Movement Disorders Criteria:
- Bilateral, symmetric postural or kinetic tremor
- Additional or isolated head tremor


Misdiagnosis

- 70 patients
- 37% misdiagnosed as Essential Tremor (ET)
- Misdiagnoses:
  - Parkinson’s disease
  - Dystonia
  - Parkinson’s disease with ET

Increased risk of false ET:
- Onset unilateral arm or leg
- Isolated head tremor
- Predominant rest tremor with mild kinetic and postural tremor

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Classic features

- Action tremor
  - Bilateral
  - Mild asymmetry common
- Postural Tremor
  - Immediate tremor
- Kinetic Tremor
  - Higher amplitude than postural tremor

- Intention Tremor
- Greater severity of action tremor
- Longer disease duration
- Head and trunk tremor
- Head tremor
- Voice tremor

Rest tremor
- 30% ET patients
- Longer duration of ET
- More severe postural and kinetic tremor

Bradykinesia
- Slow rapid successive movements
- Decreased amplitude and freezing of movements not described

Gait impairment

- Initially thought to be uncommon and age-related
- Several studies, clinical examination and laboratory setting
- Missteps during tandem gait
- Wide base, reduced speed and stride
- Posturography-impaired body sway
- Unclear effect on quality of life or falls

Arkadir and Louis. Ther Adv Neurol Disord 2013
Gait impairment

- Risk factors:
  - Older age
  - Head tremor
  - Voice tremor
  - Possibly intention tremor

- Not associated with:
  - Severity of postural or kinetic tremor
  - Unclear if age at onset or duration of disease a risk factor

Arkadir and Louis. Ther Adv Neurol Disord 2013
Neuropsychological

- Cerebellar cognitive affective syndrome
- Attention
- Executive function

- Tremor onset after age 65 → increased odds of MCI and dementia

- Diagnosis of probable Alzheimer’s disease

- Depression
- Anxiety
- Social phobias

Janicki et al. Ther Adv Neurol Disord 2013

Thenganatt and Louis.
Parkinsonism Relat Disord. 2012
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- Treatment Future Directions
ET vs. PD

- Postural tremor
  - Wrist tremor vs. MCP and phalanges
  - Flexion-extension vs. pronation-supination
- Intention tremor in 28% ET patients vs. 4% of PD patients

Re-emergent tremor
- Postural tremor with occurs at a variable latency after maintaining outstretched posture
- Same frequency as rest tremor

Sternberg et al. Front Neurol 2013
PD or PD + ET?

- A 65-year-old man with rest tremor and rigidity in the right arm is diagnosed with PD. Five years later, he develops a postural tremor of his right arm, which occurs after a latency of 10 s and a frequency similar to his 4-Hz rest tremor.

- A re-emergent tremor with similar frequency to the patient’s rest tremor is consistent with a diagnosis of PD.

- There are no additional features to suggest ET.
ET or ET+ PD?

- A 40-year-old woman with a family history of ET develops a kinetic tremor and, a few years later, a postural head tremor. Her tremor worsens considerably such that she has severe and debilitating tremor by the age of 65 years. At 70 years of age, she also develops a tremor at rest with no other features of parkinsonism.

- This patient likely only has ET with isolated rest tremor, a feature that can develop in ET cases with longstanding and severe disease.
A 45-year-old woman develops a bilateral action tremor that progressively worsens over the ensuing 15 years. Kinetic tremor is more severe than the postural tremor and she subsequently develops a postural head tremor. At 60 years of age, she develops a rest tremor in the right arm accompanied by bradykinesia (slow rapid alternating movements with loss of amplitude).

The bilateral, progressive action tremor of long duration suggests ET and development of a postural head tremor supports the diagnosis. The patient subsequently develops two parkinsonian signs, satisfying criteria for a clinical diagnosis of PD.

The patient thus has a combination of ET+PD.
Cervical Dystonia

- In ET with head tremor, hand tremor still predominant
- Isolated or predominant head tremor and minimal hand tremor

- Look for abnormal posture
- Sensory trick useful diagnostically
Task-specific tremor

- Primary writing tremor:
- Task-specific tremor
  - Either while writing or adopting the handwriting position
- Usually remains focal, but can develop a postural or kinetic component

- 56 subjects
- Progress about 10 years later to other tasks
- More refractory to pharmacologic therapy and ethanol
- Good response to deep brain stimulation

Pita et al. Mov Disord 2013.
Orthostatic tremor

- Subjective unsteadiness while standing,
- Relieved by sitting or walking
- 13 to 18 Hz in the legs, trunk; coherent in all muscles
- Auscultate with stethoscope

- Retrospective review
- 26 OT cases
- Median age of onset 61 yrs
- Symptoms usually bilateral
- Median diagnostic delay of 4.5 yrs
- Progressive course
- Associated with PD, RLS, PSP
- Treatment clonazepam

Inflammatory Neuropathies

- 43 patients with inflammatory neuropathies
- Most common in IgM neuropathy
- 58% of CIDP
- 56% of MMN with conduction block
- Mean frequency 6Hz

- Refractory to treatment
- Small number improve with treatment underlying neuropathy

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Methodological Issues

- Unknown pathology
- Mean duration of trials 5.4 weeks
- Mean number of patients 18.9
- Few studies include global clinical impression

Carranza et al. Tremor Other Hyperkinet Mov (NY) 2012.
Level A, established as effective:
  - propranolol, primidone

Level B, probably effective:
  - alprazolam, atenolol, gabapentin (monotherapy), sotalol, topiramate

Level C, possibly effective:
- Nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation

Level U, insufficient evidence:
- Gamma knife thalamotomy, pregabalin, zonisamide, clozapine

Beta-blockers

Propranolol
- Non-selective β-adrenergic antagonist
- Approximately 50% reduction
- Mean dose 185.2mg /day
- Side effects: hypotension, bradycardia, depression, sexual dysfunction

Other β-blockers
- Metoprolol, atenolol, sotalol
- Not shown to be better than propranolol

Primidone

- 50-60% tremor reduction
- Mean dose in trials 481.7mg/day
- Start at 25-50mg once daily

- Side effects most severe at onset
  - Nausea, ataxia, sedation
  - Metabolite can lower INR in patients taking warfarin

Topiramate

- Double-blind, placebo-controlled
- 200 patients, 6 months
- Mean dose 292mg/day
- Significant improvement in tremor rating scale with topiramate (29%) c/w placebo (16%)
- Significant improvement in function and disability

- Treatment-limiting side effects in 31.9% of topiramate pts and 9.5% placebo

Side effects:
- Paresthesias (5%)
- Nausea (3%)
- Concentration difficulty (3%)
- Somnolence (3%)

Gabapentin

- Monotherapy
  - 16 patients, two weeks
  - 1200mg/day
  - Improvement in tremor clinical rating scale, comparable to propranolol
  - 77% improvement in tremor measured by accelerometry

- Adjuvant therapy
  - 1800-3600 mg/day
  - Little benefit

Pahwa et al. Mov Disord 1998
Ondo et al. Mov Disord 2000.
Pregabalin

- Double-blind, placebo-controlled
- 20 participants
- 6 weeks
- 150-600 mg/day
- No improvement in clinical tremor rating scales


- Double-blind, placebo-controlled
- 29 patients
- 40 days
- 329 ± 127 mg/day
- No significant improvement in clinical scales

Zesiewicz et al. Mov Disord 2013
Zonisamide

- Double-blind, placebo-controlled
- 20 patients
- Mean dose 160±50 mg/day
- No significant improvement in clinical rating scale
- Significant improvement in tremor amplitude via accelerometry


- Evaluator-blinded, open treatment
- 25 patents
- Mean dose 252 mg/day
- Improvement in clinical rating scale

Handforth et al. Mov Disord 2009
**Sodium Oxybate**
- Open-label study, rater-blinded
- 9 patients
- Ethanol responsive
- Average dose 4.3g/day
- 6.6 point improvement in kinetic tremor (estimated percentage improvement in tremor amplitude 53%)
- SE: sedation, ataxia

**Octanol**
- 19 patients
- No difference in primary outcome of accelerometry measurements at 80 minutes
- Secondary outcome: improvement after 180 minutes


Botulinum Toxin

- Double-blind, placebo controlled
- 25 patients
- 50 units Botulinum Toxin A wrist flexors and extensors
- Additional 100 units if needed after 4 weeks
- Significant improvement in clinical rating scale, accelerometry
- No significant improvement in functional outcome
- Finger weakness

Jankovic et al. Mov Disord 1996.

- Double-blind, placebo-controlled
- 133 patients
- Botulinum toxin A 50 or 100 units, wrist flexors and extensors
- 16 weeks
- Significant improvement in clinical rating scale for postural tremor, kinetic tremor at 6 weeks
- No consistent improvement in motor tasks, functional ability
- Dose-dependent hand weakness

Brin et al. Neurology 2001
Thalamotomy

- Stereotactic procedure creating ablative lesion in ventral intermediate nucleus (VIM) of the thalamus
- Radiofrequency-generated thermal energy

Potential adverse effects:
- Dysarthria
- Hemiparesis
- Greater risk with bilateral procedures

Potential Advantages:
- Patients without access to DBS programming
- Avoid hardware complications
Thalamotomy

- 37 patients
- Mean age 70.9 years
- All patients significant improvement or complete resolution tremor immediately post-op
- Follow-up 1-13 months
- 60% no tremor, 14% mild tremor

- Recurrent tremor in 5 patients, underwent repeat thalamotomy

Complications:
- 49% (21 procedures)
- 15 patients, transient dysarthria, c/l weakness
- 6 patients (13%) with persistent side effects

Deep Brain Stimulation

- High-frequency electrical stimulation
- Disrupts cerebral motor oscillations
- Ventral intermediate nucleus (VIM) of the thalamus
- Electrodes connected to a pulse generator implanted in chest wall
Deep Brain Stimulation

Efficacy
- 60-80% improvement on clinical tremor rating scales

Loss of control over time
- Tolerance
- Progression of disease

Oliveira et al. Stereotact Funct Neurosurg 2012.

Battery Life
- 3-5 years
- Minimally invasive surgery

Rechargeable device
- 9 years
- Patient maintenance
- High patient satisfaction

Deep Brain Stimulation

Perioperative Complications
- Ischemic stroke
- Intracerebral hemorrhage
- Infection

Hardware Complications
- Infection
- Lead fracture
- Electrode malfunction
- Electrode migration

Stimulation side effects:
- Paresthesias
- Dysarthria
- Imbalance
- Dystonia
- Weakness

Gamma Knife

- External gamma radiation
- Use of neuroimaging and stereotactic frame
- No intraoperative testing
- Delayed effects of 6-12 months
- Lesion growth, permanent side effects of hemiparesis and sensory loss


- Open-label studies with positive results comparable to DBS
- One blinded study did not show significant improvement
- Considered in patients poor surgical candidates

More studies needed

Lim et al. Arch Neurol 2010
Focused Ultrasound

- Uterine fibroids, bony metastasis
- Brain tumors, thalamic pain lesions
- Focused ultrasound with simultaneous MRI imaging
- Stereotactic frame

- Similar side effects to thalamotomy?
- Decreased risk of hemorrhage and infection?
Toronto, Canada
- 4 patients
- Age 18-80
- MMSE> 24
- No history of unstable psychiatric disease

- Unilateral procedure, 5-6 hrs
- Serial lesions, increasing size
- Examination during procedure
- Low power, transient lesions to assess for side effects

- 89.4% tremor improvement at 1 month and 81.3% at 3 months
- Functional improvement in writing and motor tasks
- 1 patient with persistent paresthesias at 3 months

A Pilot Study of Focused Ultrasound Thalamotomy for Essential Tremor

- Open-label, University of Virginia
- 15 patients
- Unilateral procedure, dominant hand

At 12 months:
- Relative reduction of 75% in clinical tremor rating scale
- Relative reduction of 85% in disability
- 4 patients with persistent paresthesias

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Pathology

- Early literature:
  - Electrophysiologic entity

- Since 2000, increase in pathological studies

- Purkinje cell loss
- Torpedoes, Purkinje cell swellings
- Remodeling


Figure 3: Abnormal swellings of Purkinje cell dendrites
Genetics

**Linkage studies**
- Genetically heterogeneous
- ETM1 chr 3q13
  - Icelandic and Tajik families
- ETM2 chr 2p24
  - American (Czech) family
- ETM 3 chr 6p23

**Genome-wide association studies**
- *LINGO1*, chr 15 q
- SNP rs9652490
- Icelandic cohort
- Replicated in multiple samples
- Modest increased risk, odds ratio 1.2–1.7

Testa. Tremor Other Hyperkinet Mov (N Y) 2013.