TREMORS

Gerald Calegan, MD

Chairman, Dept of Neurology

Movement Disorder Neurologist

The NeuroMedical Center

Baton Rouge, LA

Tremors

- Most common form of involuntary movements.
- Definition – rhythmic, oscillatory, repetitive movement , produced by alternating or synchronous contractions of antagonist muscles.
- Also defined as rhythmic oscillation of at least one body region.

- Classification is by :
  - Distribution – according to the body part affected
  - Pattern of occurrence – rest, postural, action or kinetic, task specific
  - Tremor frequency (although considerable overlap)
  - Etiology

CATEGORIZATION OF TREMORS

REST TREMORS	ACTION TREMORS		
	POSTURAL	KINETIC	MISCELLANEOUS
•Parkinsonian •ET variants (especially long-standing ET)	•Physiologic •Enhanced physiologic (stress, drugs, endocrine) •Essential Tremor (ET) •Orthostatic •PD (re-emergent) •Dystonic •Cerebellar	•ET •Cerebellar lesions as in MS, stroke, wilson disease, •Task specific •Dystonic •Cerebellar	•Idiopathic •Psychogenic •Other involuntary movements like Asterixis, Clonus, Phasic spasticity

TREMOR RATING

0 – none perceived

1 - slight (barely noticeable)

2 - moderate, noticeable, probably not disabling (<2cm excursions)

3 - marked, probably partially disabling (2-4cm excursions)

4 - severe , coarse, disabling (> 4 cm excursions)

PATHOPHYSIOLOGY OF TREMORS

- Four different mechanisms have been proposed :

1. Mechanical oscillations of the extremity
2. Reflexes eliciting and maintaining oscillations
3. Central oscillators functioning abnormally
4. Tremulous central motor command because central feed-forward or feedback loops are altered

REST TREMORS

- Most typically seen in Parkinson disease patients.
- PD rest tremor usually initially unilateral
- Tremor-dominant PD associated with-
    - Earlier age of onset
    - Less cognitive decline
    - Slower progression than the Postural instability and Gait difficulty (PIGD) variant.
- 20% of PD patients have no significant tremor

PARKINSONIAN TREMOR

- **Rest tremor** in upper limb, fingers and hand :
  - Pill rolling 3-5Hz
  - Usually asymmetrical (b/c unilateral at onset)
  - Abolishes by movement but may reappear in new posture (Re-emergent tremors)
  - Leg, tongue, lip and jaw may also be involved
  - Exacerbation by emotional stress
  - Response to antiparkinsonian drugs

PARKINSONIAN TREMOR

- **Postural, Action tremor** upper limb tremor:
  - Frequency usually 6-8 Hz

PARKINSON'S DISEASE TREATMENT

- **Carbidopa/Levodopa is by far most potent drug for PD, with least side effects relative to potency**
- **Other meds include:**
  - **Dopamine agonists (pramipexole, ropinirole)**
  - **Half-life extenders of levodopa (entacapone, rasagiline, others)**
  - **others: amantadine, anticholinergics**

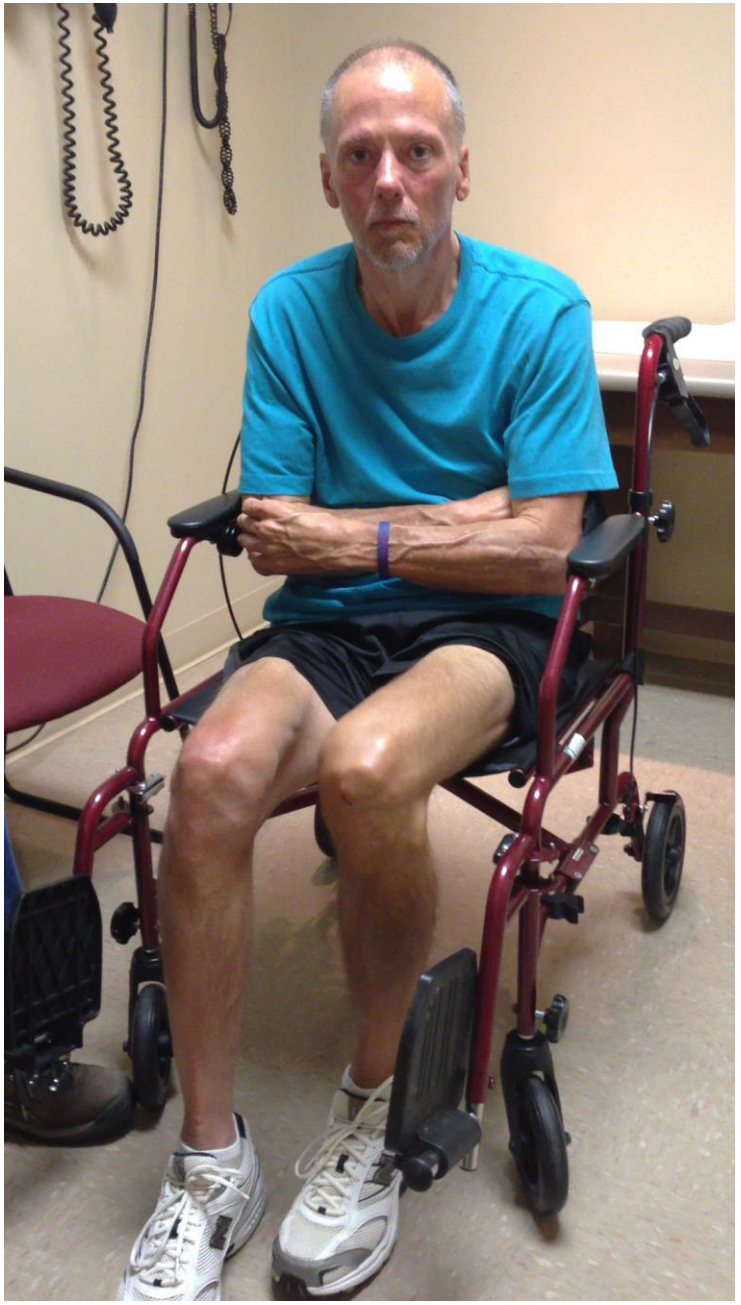
PARKINSON'S DISEASE TREATMENT

- **Surgical therapies indicated when:**
  - **difficult to control symptoms (especially on/off fluctuations and dyskinesias) with medications,**
  - **or when too many medication side effects to optimize dose of medications**
  - **High amplitude rest tremor (requires very high doses of medications)**

PARKINSON'S DISEASE TREATMENT

- **Surgical therapies:**
  - **Deep Brain Stimulation (DBS)**
    - **Target is subthalamic nucleus (STN) or Globus Pallidus internus (GPi)**
    - **Invasive (burrhole) but non-destructive**
    - **Most often done bilaterally**
  - **Focused Ultrasound (FUS)**
    - **Target: GPi or thalamus**
    - **Typically only done unilaterally**
    - **Non-invasive but destructive (creates a lesion)**
    - **One-time therapy**

TREMOR DOMINANT PARKINSON DISEASE BEFORE TREATMENT



TREMOR DOMINANT PARKINSON DISEASE AFTER TREATMENT

PARKINSON'S DISEASE TREMOR WITH DBS ON/OFF

ENHANCED PHYSIOLOGIC TREMOR (EPT)

- Rapid 8-12 Hz small amplitude, fine postural and kinetic tremors
- Difficult to distinguish from ET (but ET is progressive)
- Typically affects upper limb and hands
- Etiology :
  - Exaggerated physiological response – anxiety, fatigue, fright, sternous exertion
  - Drugs like amphetamines, amiodarone, caffeine, valproate, theophylline, thyroxine, alcohol withdrawl
  - Metabolic – hypoglycemia, pheochromocytoma, thyrotoxicosis

ESSENTIAL TREMOR (ET)

- No known cause (Idiopathic)
- Prevalence 1-3% of population
- 1% age 18-30, up to 10% in elderly
- Slowly progressive
- Family history in 50% cases.
- Hereditary factors also involved (Autosomal dominant inheritance) , responsible genes not known
- Age of onset : Bimodal, young adults and 40-60 years
- Can cause marked physical and psychosocial disability.
- Amplitude increases and frequency decreases with age

ESSENTIAL TREMOR (ET)

- ET is typically a postural or kinetic/action tremor of fingers, hands and forearms when held outstretched, during specific fine motor tasks.
- Other sites – head (30-40%), voice (15-20%)
- Frequency 4-10 Hz.
- Bilateral, may be asymmetric
- No other neurological signs (except mild balance impairment)
- Frequency is relatively constant while amplitude may vary
- Improves by alcohol in 50% cases.

ESSENTIAL TREMORS (ET)

- No characteristic pathologic, biochemical, or radiological findings
- No workup required, but may want to screen for hyperthyroidism

EVIDENCE BASED RECOMMENDATIONS FOR TREATMENT OF ESSENTIAL TREMORS (by AAN subcomittee)

- Propranolol and Primidone reduces limb tremor (Level A)
- Alprazolam, atenolol, Gabapentin, Sotalol and Topiramate (Level B)
- Propranolol reduces head tremor (Level B)
- Clonazepam, clozapine, Nimodipine (Level C)
- Botulinum Toxin A in limb, head and voice tremor (Level C)
- Thalamic (VIM) DBS and Thalamic Focused Ultrasound (Level C)
- Gamma knife Thalamotomy (Level U)

TREATMENT OF ESSENTIAL TREMOR

- Treatment mainly depends on severity.
- Many patients require reassurance.
- Many patients consume alcohol for its calming effect and prophylactically too (60 ml 10-15 mins prior to anticipated event to avoid embarassment).
- Alcohol – central effect – potentiates GABA activity.
- But regular alcohol consumption – NOT recommended.
  - Rebound worsening of tremor after alcohol metabolized
- Long term alcohol consumption – may have substantial risk of developing ET (cerebellar toxicity)

- Drugs mainly reduce tremor amplitude with no effect on tremor frequency.
- Large amplitude and slow frequency tremor – usually do not respond well to pharmacological therapy.
- **PROPRANOLOL** – beta-blocker – most effective drug for ET and enhanced physiologic tremors.
  - less effective in head tremors.
- Therapeutic effect may be mediated by peripheral beta adrenergic receptors.
- DOSE – 20-60 mg/day initially, increase to 120 mg/day

- PRIMIDONE
  - also reduce limb tremors.
  - Started at low dose (25mg HS) to avoid acute idiosyncratic reactions (nausea, vomiting, confusion, ataxia)
  - dose > 250 mg are usually not required.
  - no head to head comparisions with Propranolol.
- BENZODIAZEPINES (Clonazepam, Lorazepam, Alprazolam)
  - Habit-forming; usually need escalating doses

ESSENTIAL TREMOR TREATMENT

- **Surgical therapies:**
  - **Deep Brain Stimulation (DBS)**
    - **Target is VIM subnucleus of thalamus**
    - **Invasive (burrhole) but non-destructive**
  - **Focused Ultrasound (FUS)**
    - **Target: thalamus**
    - **Typically only done unilaterally**
    - **Non-invasive but destructive (creates a lesion)**
    - **One-time therapy**

TREATMENT OF ESSENTIAL TREMOR

- **DBS indicated when trials of propranolol and primidone fail or provide inadequate treatment**

ESSENTIAL TREMOR TREATMENT WITH DBS ON/OFF

DBS notes

- **Contraindications:**
  - **Dementia (get neuropsychological testing)**
  - **Severe Depression**
  - **Frequent falls**
  - **For PD: no response to levodopa (atypical PD such as Multiple System Atrophy, Progressive Supranuclear Palsy**

DYSTONIC TREMORS

- Asymmetrical postural, kinetic and rarely rest tremors
- Occurs in association with focal or generalized dystonias
- Frequency 2-6 Hz
- CAN BE INDISTINGUISHABLE FROM PARKINSONIAN TREMOR
  - But PD patient will have other symptoms

IMPORTANTANT TREMOR CONCEPTS

- Parkinson's Disease is primarily REST tremor
- Essential Tremor is primarily ACTION tremor
- PD and ET both can have POSTURAL tremor
  - But in PD, postural tremor often delayed
- PD and ET most commonly misdiagnosed as the other
- Longstanding PD: tremors can intrude into action
- Longstanding ET: tremors can intrude into rest

IMPORTANTANT TREMOR CONCEPTS

- Isolated Head tremor (without hand tremors) can be ET or dystonic tremor (Cervical Dystonia)
- Cervical Dystonia often has twisting/turning component (abnormal head position)
- No biomarkers to distinguish
- ET may respond to alcohol
- Both respond to botulinum toxin injections
- And, CD may spread regionally and cause complex hand tremors

ORTHOSTATIC TREMOR

- Fast tremor (14-16 Hz), involving mainly legs and trunk when standing still (often not really visible)
- Often associated with a feeling of unsteadiness and calf cramps
- Relieved by walking, sitting or supine position
- Exact pathophysiology not known
- Some consider it a variant of ET
- SPECT shows marked reduction of dopamine transporters.
- No response to conventional anti ET drugs
- May improve with Clonazepam and Gabapentin
- Some respond to Levodopa or Levetiracetam

Cerebellar Tremors

- Typically associated with lesions or diseases that involve cerebellum or its outflow pathways (MS, stroke, tumors)
- Coarse, low frequency tremor 5 Hz
- Kinetic tremor w/ intention component
  - intention is increased amplitude as target approached
- May also exhibit postural tremors and titubations of head/trunk

- No drug has shown to reduce cerebellar tremor satisfactorily.
- Attaching weights to wrist may have limited improvement.
- VIM (thalamic) DBS can help, but rate of success much lower than ET

PSYCHOGENIC TREMORS

Koller & colleagues (1989) gave the following diagnostic criteria :

- Abrupt onset
- Static course
- Spontaneous remission
- Difficult to classify into a subtype
- Selective disability
- Changing amplitude and frequency
- Unresponsive to drugs
- Increasing of tremor with attention and decrement with distraction
- Responsiveness to placebo
- Absence of any other neurologic signs
- Response to Psychotherapy

NEUROPATHIC TREMORS

- Postural, kinetic tremor, upper limbs > lower limbs
  - Coarse flapping (3-6 Hz)
  - Most commonly described in association with demyelinating neuropathy (Ig M paraproteinemia, CIDP)
  - Signs of neuropathy (muscle wasting, Weakness, areflexia, sensory loss)
  - My hypothesis: just ET plus neuropathy??
  - Treatment: same as ET

ISOLATED TASK SPECIFIC OR POSITION SPECIFIC TREMORS

- Kinetic tremors during specific tasks (6 Hz)
- Upper limb : occupational tremors (musicians), primary writing tremors
- Head and lips : musicians (wind instruments)
- Task specificity is characteristic.
- May respond to anticholinergics, clonazepam, botulinum toxin.
- My hypothesis: dystonic tremor?

THANK YOU

ESSENTIAL TREMOR

CEREBELLAR TREMORS

DYSTONIC TREMORS

NEUROPATHIC TREMORS

TASK SPECIFIC TREMORS / PRIMARY WRITING TREMORS

WING BEATING TREMORS

ORTHOSTATIC TREMORS

PSYCHOGENIC TREMORS