Tremor

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Objectives

- Classification and epidemiology of tremors
- Identification of tremors: clinical features, diagnostic and clinical testing
- Differentiation between Essential tremor and Parkinson’s tremor
- Management of tremor
Disclosures

- None
Movement disorder

- Hyperkinetic or Hypokineti

- Hypokineti disorders: Parkinson’s disease, Parkinson plus syndromes (PSP, MSA etc), Hypothyroid, Hypoparathyroid, Toxic etc

- Hyperkinetic disorders: Tremor, Dystonia, Chorea, Dyskinesias, Tics, Myoclonus, Athetosis, Ballismus.
Tremor

- Tremor is the most common abnormal involuntary movement disorder.

- Tremor is an involuntary, rhythmic/repetitive, oscillatory movement produced by alternating or synchronous contraction of reciprocally innervated antagonist muscles.

- Frequency is fixed, amplitude may vary.

- Tremor can occur in isolation or as part of clinical syndrome.
Classification of Tremors

• Based on positional properties: Rest or Action or Task specific

• Rest tremor: occurs when limb is fully supported against gravity and the muscles are not voluntarily activated. It decreases with voluntary action. (Parkinson tremor)

• Action Tremor: present during the voluntary contraction of muscles

• If it is Action Tremor sub classify as:
  • Postural: evident when anti-gravity posture is maintained (ET, Cerebellar)
  • Kinetic: occurs during voluntary active movement (ET, Cerebellar)
  • Intention: exacerbated toward the end of goal-directed movement (Cerebellar tremor)
  • Isometric: present during voluntary muscle contraction not accompanied by movement (orthostatic tremor)
Classification of Tremors

- Rest Tremor: Parkinson’s disease, Drug induced Parkinsonism (neuroleptics, phenothiazines, Metoclopramide, Lithium), Parkinson plus syndromes (less common), Long standing ET, Wilson’s disease

- Action Tremors:
  - Postural: Physiologic/Exaggerated physiologic tremor, ET, Drug induced (Lithium, Amiodarone, Beta adrenergic agonist), EtOH withdrawal, Psychogenic, Post-traumatic, Heavy metals, Metabolic disorders (Thyrotoxicosis, Pheochromocytoma, Hypoglycemia), Neuropathic tremor, Orthostatic
  - Kinetic: Cerebellar lesions and all the above examples of postural tremor
  - Intention: Cerebellar lesions
Drugs/Toxins commonly associated with Tremor

- Alcohol (chronic use or withdrawal) & Benzodiazepine withdrawal
- Anti-arrhythmic drugs: Amiodarone, Procainamide
- Antiepiletics/mood stabilizers: VPA, CBZ, Lithium
- Tricylic antidepressants and SSRIs (Fluoxetine)
- Immune suppressants & Anti-virals: Cyclosporine, Tacrolimus, Acylovir, Vidarabine
- Stimulants & Astma Rx: Amphetamines, Albuterol, Caffeine, Cocaine, Nicotine, Albuterol, Theophylline
- Cholinesterase inhibitors: Donepezil, Rivastigmine etc
- Heavy metals: Mercury, lead, arsenic
- Miscellaneous: Metoclopramide, Neuroleptics, Lithium (all three can also cause extrapyramidal signs). Too much Levothyroxine, Atorvastatin, Prednisone, Nifedipine
Clues to Clinical diagnosis

- History: Age of onset, Mode (sudden or gradual), anatomical site, rate of progression to other sites, alcohol responsiveness, hx of alcohol abuse, family history

- Review of medications

- Neurological examination: bradykinesia, rigidity, nystagmus, scanning speech, ataxia, wide variation of tremor frequency

- Presence of head tremor (titubation): ET; dystonic tremor/cervical dystonia; cerebellar outflow tremor (MS, posterior fossa disorders)

- Tremors starting in unilateral arm and migrating to ipsilateral leg: usually Parkinson’s tremor

- Limitations: eating with spoon, signature on check, cursive to print writing, voice changes, pouring tea etc; compensatory mechanisms?; micrographia
Clinical Assessment

- Anatomical localization: UE/LE, head, chin, lip, jaw, trunk, palate
- Activation condition: Rest, posture, specific task
- Frequency: low (<4 Hz), medium (4-7 Hz), high (> 7 Hz)
- Amplitude
- Spiral drawing, wavy line drawing and straight line between two straight lines drawing with both hands. Writing sample.
- Dot approximation task: makes action tremor worse/overt
- Finger nose finger, Heel to shin test, Gait (upper limb rest tremor worsens while postural ET tremor subsides)
Clinical Assessment

A  Spiral and line drawings by patient with essential tremor (case 1)

- Untreated
- Propranolol treatment
- Suppression with alcohol

B  Handwriting samples from case patients

Patient with essential tremor (case 1)
This is a sample of my best hand writing

Patient with Parkinson disease (case 2)
There is my best handwriting.
Investigation for Tremor

- A laboratory workup is not necessary for most tremors

- Postural or action tremor: TSH, 24 hr urine for heavy metals, comprehensive metabolic panel

- Young patients (< 50 yrs): r/o Wilson’s disease- serum copper and ceruloplasmin, 24 hr urine copper, slit lamp examination

- Asymmetric cerebellar or postural tremors: neoplasm, stroke, demyelinating lesion: Imaging with MRI Brain (non contrast)

- Rest/Parkinsonian tremor, Cerebellar tremor: MRI brain

- ET or PD: DaT Scan

- Accelerometer, Surface EMG
Physiologic Tremor

- Physiologic Tremor: Very low amplitude fine tremor (6-12 Hz), barely visible to naked eye and is present in everyone.

- Enhanced Physiologic Tremor: Visible tremor that is present when a particular posture is maintained. Anxiety, stress, fear, exercise, fatigue, alcohol withdrawal, hypoglycemia, thyrotoxicosis, drugs, toxins, pheochromocytoma can precipitate this.

- Rx: Remove the exacerbating factor. Beta blockers
(Benign) Essential Tremor

- Most common movement disorder. Around 2.2% (0.4-6%) of US population. No sex or racial difference

- Bimodal distribution at 15-20 and 50-70 year age

- “Essential” means there is no other cause for tremor and there are no other neurological signs

- Positive family history (AD trait in 60%) and striking improvement with EtOH (30 min-several hours) in 50-90% patients.

- Worsens with stress, anxiety, emotions, fatigue, cold temperature

- When severe, it may persist in rest making distinction from Parkinson’s tremor difficult.
(Benign) Essential Tremor

- Starts distally in the arms: flexion-extension motion at the wrists OR abduction-adduction motion of fingers

- Persistent, bilateral (may start unilaterally also), likely symmetrical, postural/kinetic tremor of hands or arms (absence of any latency) or head (na-na type). 4-8 Hz. May worsen further at the end of goal-directed movement

- Hands > head > voice > legs > chin

- May be associated with other movement disorders: cervical dystonia, writer’s cramp, spasmodic dysphonia.
Essential Tremor

Treatment

- **Propranolol**: Beta adrenergic receptor agonist. 120-320 mg daily in 3-4 divided doses or 60-80mg ER. Start at 40 mg bid or 60mg ER and increase weekly monitoring BP and HR. Assess for any contraindication e.g. conduction block, heart failure, asthma etc. A/E of fatigue, nausea, depression. Do not stop abruptly due to rebound hypertension. Effective 60-70%. Dropout rate 20%

- Other Beta blockers: Metoprolol (when asthma present), Atenolol, Timolol, Nadolol (fewer CNS side effects).

- **Primidone (Mysoline)**: Phenobarbital analogue. 50-250mg, start at night time with 25 mg and titrate by 25 mg weekly. A/E of drowsiness, nausea, vertigo, unsteadiness, flu-like symptoms. Maximum dose of 750mg divided three times daily. 20% of patients can have acute idiosyncratic reactions which resolves in 2-3 days. Dropout rate of 20-30%

- Try dual therapy if side effects tolerable

- Propranolol and Primidone most effective for hand tremor
Essential Tremor 
Treatment

- Topiramate (150-300 mg daily as bid), Gabapentin (1200-3600 mg daily as tid), Lyrica (150-600 mg daily as tid); Benzodiazepines e.g Clonazepam (short term and prn use), Botulinum toxin (smaller effect on intention component), acetazolamide

- 30-50% of ET patients may not respond to medical therapy. DBS of thalamus (ventral intermediate nucleus), FDA approval in 1997; Reduction of extremity tremor > midline tremor. Does note help balance.

- Stereotactactic ablation

- Alternatives: Biofeedback or behavioral therapy, OT/adaptive devices
Parkinson’s Tremor

- Rest tremor of 4-6 Hz. Many patients have combination of slower resting and faster postural tremor (at later stage)

- Flexion-extension of fingers AND abduction-adduction of thumb gives the classic “pill rolling”. Action or postural tremor (re-emergent tremor) at later stage of disease. 10% of Parkinson’s disease never have any tremor.

- Usually there is no family history and alcohol does not have any affect

- Hands, legs, lips, jaw, chin, tongue. Rarely involves the head.
Parkinson’s Tremor

- Starts intermittently on one side (arm), gradually becomes more persistent and then migrates to other side in few years of time.

- Similar exacerbating factors as ET

- Increase prevalence > 60 yr age.

- Other features: Bradykinesia, Rigidity, Postural instability, Decreased arm swing, Micrographia, Masked facies/apathetic look, Anosmia etc
Video

IMG_1845.MOV

IMG_1766.MOV
Parkinson’s tremor treatment

- If age > 70 years: Carbidopa/levodopa (Sinemet): Inhibits peripheral dopamine decarboxylation. Most effective overall.

- However, it is associated with complications of motor fluctuations, LIDS (levodopa induced dyskinesias). Start with regular preparation and not CR (controlled release). Start at 10/100 or 25/100 mg tid for a week and then titrate as needed. A/E of nausea, vomiting, dizziness

- works best when taken empty stomach. Protein interferes with absorption

- Entacapone (Comtan): Selectively inhibits COMT (catechol-O-methyltransferase) 200mg bid-qid. To be given along with each Sinemet dose to increase central bioavailability of levodopa. Assess for hepatic impairment.
Parkinson’s tremor treatment

- If age < 70 years: Dopamine agonists e.g. Pramipexole (0.5-1.5 mg tid), Ropinirole (3-6 mg tid) 3-4x/daily. A/E of nausea, dizziness, confusion, excessive sleepiness, obsessive compulsive behavior. Always start with low dose.

- Dopamine agonist patches: Neupro/Rotigotine (2-8 mg/24 hr patch);

- Use of Ropinirole is associated with higher risk of hypotension, somnolence. Use of Pramipexole is associated with higher risk of hallucination

- Anticholinergics: Artane (Trihexyphenidyl), Benztropine: can improve only tremor and not other symptoms of PD. Adjunctive therapy. A/E of sedation, blurry vision, dry mouth, urinary retention, cognitive difficulties in elderly. 2-12 mg daily

- Amantidine: Start at 100 mg daily (old age or if taking other PD medications) or twice daily. Works best for PD associated dyskinetic movements, drug induced parkinsonism
Parkinson’s tremor treatment

- MAO-B inhibitors: Selegeline (5 mg bid), Rasagiline/Azilect (1 mg once daily). Can be used early as mono therapy or at late stages to reduce “off time”. Neuroprotection ??


- Thalamus (tremor), Globus pallidus interna (GPI) and sub-thalamic nuclei (STN) (helpful for all cardinal features of PD)

- Criteria for DBS referral: Idiopathic PD; Troublesome motor symptoms despite appropriate Rx/intolerable A/E; Clear motor improvement with levodopa; absence of dementia, moderate to severe depression or significant medical conditions that prevent surgery
# ET and Parkinson’s Tremor

<table>
<thead>
<tr>
<th></th>
<th>Parkinson’s Tremor</th>
<th>ET</th>
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<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Resting tremor</td>
<td>Postural/action</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>&gt; 60 yr</td>
<td>All age groups</td>
</tr>
<tr>
<td><strong>Family Hx</strong></td>
<td>Usually negative</td>
<td>Usually +</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>Not beneficial</td>
<td>Beneficial</td>
</tr>
<tr>
<td><strong>Tremor onset</strong></td>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td><strong>Limb Tone</strong></td>
<td>Cogwheel</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Facial expression</strong></td>
<td>Apathetic</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Gait</strong></td>
<td>Festinant, arm swing</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Tremor latency</strong></td>
<td>Longer: 8-9 sec</td>
<td>Shorter: 1-2 sec</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Slow (4-6 Hz)</td>
<td>Rapid (4-8 Hz)</td>
</tr>
<tr>
<td><strong>Writing</strong></td>
<td>Micrographia</td>
<td>Tremulous</td>
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</table>
ET and Parkinson’s Tremor

- High level of misdiagnosis of ET and PD. Diagnosis of ET overused, even among neurologist. Misdiagnosis is more frequent in elderly

- About 1 in 3 patients misdiagnosed as having ET with most commonly missed diagnosis of PD and dystonia. Most common associated factor misdiagnosed with ET were unilateral arm tremor, dystonic posturing, isolated thumb tremor

- ET does not progress to PD. Some patients can have both! or have overlapping features.

- 3% of ET cases develop PD symptoms after median f/u of 3.3 years compared to 0.7% of control.

J Neurol 2000: 955-59
Age aging 1999: 99-102
Arch Neurol 2006: 1100-04
J Neurol Neurosurg Psych 2009: 423-25
ET and Parkinson’s Tremor

- Rest tremor can be seen in 20-30% of patients with ET (sever disease and longer duration)

- While action/postural tremor is hallmark for ET, it is found in PD patients as well. Look for clues of re-emergent tremor. Kinetic tremor is of greater amplitude than postural tremor in ET whereas converse in PD.

- Action tremor in ET is often but not necessarily bilateral. Side to side variation is common.

- Head tremor can at time be seen in PD patients. In ET head tremor resolves on lying supine (rest)

- Jaw tremor may occur in ET also and is more a postural or kinetic

- Bradykinesia may be observed in some ET patients but lack freezing
DaT-SPECT Scan

- Helps differentiating ET and PD tremors

- DaT (Iofluopane I-123)-SPECT scan may be useful but lack high specificity (98% sensitive and 83% specific).

- Radiopharmaceutical imaging that works by binding striatal dopamine transporter (DaT) in brain providing visual imaging of density of DaT

- Missouri: SLU, Mercy-Springfield, University of Kansas

- [http://us.datscan.com](http://us.datscan.com)
I-123 DaTscan SPECT

DaTscan image in an age-matched healthy control

DaTscan image in a confirmed PD patient
**Basics of Image Interpretation**

**Normal:**
Two symmetric comma- or crescent-shaped focal regions of activity

**Abnormal:**
Activity is asymmetric

**Abnormal:**
Activity is absent in the putamen of both hemispheres and confined to the caudate nuclei

**Abnormal:**
Activity is absent in the putamen of both hemispheres and greatly reduced in one or both caudate nuclei

Cerebellar Tremor

- Diseases of cerebellar outflow: dentate nuclei, interpositus nuclei, superior cerebellar peduncle

- Low frequency (< 4Hz) postural and kinetic tremor with prominent intention component. Coarse side-to-side component. Occurs throughout the movement but worsens at the end of target. Amplitude of tremor increases as limb is extended.

- Ipsilateral arm (oscillation around the shoulder) or leg (oscillation around the hip) when cerebellar hemisphere is involved; isolated postural tremor of head (titubation)/trunk with cerebellar vermis degeneration (less commonly can present as bilateral hand tremor).

- Other associated symptoms: ataxia, dysarthria, dysmetria, dysdiadochokinesia

- Stroke, tumor, MS, vitamin E deficiency, paraneoplastic syndrome, alcoholic cerebellar degeneration, mercury toxicity

- No particular medication useful. Can try Rx for ET or clonazepam and if that fails can try Thalamic DBS
Psychogenic Tremor

- Not rare.

- Variability in tremor amplitude and frequency. Can involve any part of the body. Can present with unusual combination of postural, resting and action tremors

- Increases in severity with attention & decreases with distraction. If affected limb is restrained, the tremor may move to another part of body.

- Sudden or abrupt onset, variable course with spontaneous remission. Ability to perform some function despite severe tremors

- False signs on examination: give away weakness, bizarre sensory findings. Can have multiple psychosomatic complaints.

- Unresponsiveness to medications. Psychotherapy is the main treatment.
Primary Orthostatic Tremor

- Shaky leg syndrome

- Variant of ET. Occurs in legs and trunk immediately on standing and relived by sitting, walking.

- Usually high frequency: 13-18 Hz. No other clinical signs.

- Rx: Clonazepam (drug of choice), Pramipexole, Primidone

- Orthostatic tremor plus: other neurological disorders also coexist such as PD, ET, RLS, peripheral neuropathy etc
Other Tremors

- **Post-traumatic**: after head trauma, 4-6 Hz, few months after injury, proximal and increases with movement. Rx: Propranolol

- **Neuropathic tremor**: demyelinating, hereditary (CMT), IgM paraproteinemias, DM, Anterior horn cell disorders, porphyria. Clinically similar to ET.

- **Mid-brain/Rubral/Holmes tremor**: irregular, low frequency 4.5 Hz, wing beating tremor persisting in all positions (present at rest, increases with posture and worsens further with intention/action). Etiology: Stroke, MS. Delay of 2 week-2 years in tremor onset. Intention > Postural > Rest
Video
Other Tremors

- **Dystonic Tremor (DT):** Postural/kinetic tremor that resembles ET or an enhanced physiologic tremor and a tremor that is a rhythmic expression of rapid, dystonic movements.

- Irregular amplitude and variable frequency (< 7Hz).

- Worsens when the patient voluntarily moves the affected body part against the major direction of pulling caused by dystonia (e.g. patient with right torticollis may have more tremor when he turns the head towards left)

- Disappears with complete rest. May disappear with ‘sensory tricks’ such as touching the affected body part/muscle

- Dystonic head & neck tremor, limb tremor, vocal tremor

- Treatment: Anticholinergics (Trihexyphenidyl 4-10 mg), Botox, Clonazepam, ET Rx

- **Tremor associated with Dystonia (TAD):** Present in body region not affected by dystonia. Symmetric, postural and kindest tremor typically of higher frequency.

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# Recommendations for clinical practice

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<tr>
<th>CLINICAL RECOMMENDATION</th>
<th>EVIDENCE RATING</th>
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<tr>
<td>A comprehensive review of medications (prescribed and over-the-counter), with specific attention to medications started proximal to the onset of tremor, is important in patients with new-onset tremor.</td>
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<tr>
<td>The diagnosis of tremor is based on clinical information obtained from a thorough history and physical examination.</td>
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<tr>
<td>A rest tremor is usually caused by parkinsonism.</td>
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<td>Tremor in children is potentially serious; patients should be promptly referred to a neurologist.</td>
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<tr>
<td>For particularly difficult tremor cases, single-photon emission computed tomography to visualize the integrity of the dopaminergic pathways in the brain may be useful to diagnose Parkinson disease.</td>
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</tr>
</tbody>
</table>
Resources

Essential Tremor. NEJM 2001


Diagnosis and Management of the Patient with Tremor. Medicine and Health 2004

Differentiation and Diagnosis of Tremor. Am Fam Physician 2011


Psychogenic Tremors. Neurology 1989

Mini Reviews: Linkages between essential tremor and Parkinson’s disease? From Cell Neurosci 2013


www.movementdisorders.org
www.parkinson.org

Distinguishing essential tremor from Parkinson’s disease: bedside tests and laboratory evaluations
Mary Ann Thenganatt and Elan D Louis