Clinical Evaluation of Neurological Tremors: Focus on Essential Tremor

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Lecture Outline

- I. Definitions
- II. Types of Tremors
- III. Diagnosis of essential tremor
- IV. Medical Treatment of essential tremor
- V. Non-medical treatment of essential Tremor
- VI. Treatment of other types of tremor

I. Definitions

- A tremor is a rhythmic, oscillatory fast movement of a limb or the head
- There are different types of tremors
- For each type of tremor, there are different causes or etiologies
- Treatment depends on the type of tremor

II. Characterizing Tremors Into Types

- The first step in evaluating a patient with tremor is to characterize the tremor *type*. This relies on a careful history and neurological examination of the tremor.
- The second step is to determine the *etiology*
- The three major types of tremor are:

  -Action/postural

  -Resting

  -Intention

IIa. Action/Postural

- Occurs in the context of performing action or maintaining a posture (for example, sustained extension) of a limb
- The tremor is usually bilaterally symmetric
- Also occurs during voluntary motion such as writing, eating – hence the term action/postural
- When severe, this type of tremor could be disabling
- There are different etiologies of action/postural tremor, with the most common being essential tremor

IIb. Resting Tremor

- Occurs at rest (when the limb is relaxed and stationary) and stops with movement (unlike A/P tremor)
- Could occur while the person is sitting, standing or walking
- Typically, is asymmetric, involving either an arm or leg
- Asymmetric resting tremor – in combination with bradykinesia and rigidity – is a major presenting symptom of Parkinson's disease

IIc. Intention Tremor

- This is also known as cerebellar tremor
- The tremor movement classically begins as the finger approaches a target (for example during finger-to-nose testing)
- It is often accompanied by other hallmarks of cerebellar disease such as ataxic gait, scanning speech, etc…
- However, an intention component could accompany action/postural tremors

III. Essential Tremor – *Epidemiology*

- Essential tremor is the most common cause of action/postural tremor.
- Prevalence estimates range from 0.4 to 6% and increase with advancing age (Louis et al., 2001).
- It is characterized by the presence of both action>postural tremors (always of the hands and sometimes also involving the head, lower limbs, voice, face/tongue or trunk).
- There is a family history in 30-50% of cases, yet specific genetic factors have not been identified
  - Having a first degree relative with ET makes it 4.7 times more likely to develop ET

Benito-Leon and Louis, 2012

III. Diagnosis of Essential Tremor

- ET is a clinical diagnosis
- Differential diagnosis includes: Enhanced physiological tremor, Parkinson's disease (A/P tremor could be present), idiopathic dystonia, Wilson's disease, orthostatic tremor, cerebellar tremor, psychogenic tremor, Fragile X tremor-ataxia, peripheral neuropathy-relate tremor, hyperthyroidism, etc.
- The tremor is largely isolated in essential tremor, whereas other symptoms and signs co-exist with tremor in these other conditions
- Temporary amelioration with alcohol is a distinguishing factor of essential tremor, though not very specific

III. Physiological Tremor is in the Differential of Essential Tremor

- We all have rhythmic oscillatory movements of the hands, even if not apparent to the naked eye. This tremor is observed as an action/postural tremor.
- Even when not obvious on exam, this could be detectable with electrophysiological techniques.
- Stressful circumstances and certain medications and medical conditions may enhance this type of tremor and make it visible.
- Physiological tremor is NOT progressive over time, in contrast to other "pathological" tremors including ET.

III. Proposed Diagnostic Criteria of Essential Tremor

- Definite ET:
  - Action tremor of moderate amplitude in at least one arm during at least four tasks
  - Tremor must interfere with at least one activity of daily living
  - Other causes of A/P tremor are eliminated
- Probable ET:
  - Action tremor of moderate amplitude in a least one arm during at least four tasks
  - Other causes of A/P tremor are eliminated

Louis et al., 2001; *Ann Neurol*

III. Essential Tremor – *Etiology*

- The etiology of ET remains mysterious.
- Early on, it was thought to be a peripheral, neuromuscular condition
- A central localization is now undisputed
- Pathophysiology involves circuitry spanning the basal ganglia of the brain and the cerebellum
  - Hypothesis of cerebellar Purkinje cell dysfunction. Reduced function of these GABA-producing cells results in a tremor-promoting dis-inhibition
  - Alcohol, a known toxin to cerebellar Purkinje cells, is a known causative risk factor

Thenganatt et al., 2012

III. Essential Tremor – *Not so Benign*

- Although in the past described as "benign", because the condition is limited to tremor, the tremor could be quite disabling – as it affects the hands while in active use – and is gradually progressive over time
  - Usually is either late onset with progression or early onset with delayed progression
- About 15-25% of patients with ET have a functionally significant impairment

Bain et al., 1994

Case 1

- A 37-year-old man presented with recent onset “tremulousness” of both hands that occurs in the context of activity (such as holding utensils to eat). The onset of the tremor appeared to coincide with starting a medication, valproic acid, to treat recently diagnosed epilepsy. On exam, the only finding was of a mild/moderate bilaterally symmetric action/postural tremor.

- What is the type of tremor?
- What is the etiology of the tremor?

Case 2

- A 56-year-old woman presented for evaluation of tremors of the hands and of head "bobbing" that have progressed over the last 20 years to the point where she could no longer write legibly. There is a family history of similar tremors on her father's side. She is concerned that her symptoms may be due to Parkinson's disease. On exam, she has a moderate/severe action tremor of the bilateral arms (right slightly more pronounced), and evidence of a side-to-side tremoring of the head. There is no evidence of rigidity, resting tremor, hypomimia, or bradykinesia. She has a negative evaluation for hyperthyroidism and for Wilson's disease.

- What is the type of tremor?
- What is the etiology of the tremor?

Case 3

- A 79-year-old man presented to his primary care physician's office with a six-month history of difficulty using his right hand. He described himself as becoming less "limber" on that side, and his family described intermittent shaking of the right hand. There is no history of current or past neuroleptic use. On exam, he had reduced facial expression (aka hypomimia), an intermittent tremor only of the right hand that transiently stopped when he performed tasks with the hand; in addition, he had subtle bilateral fine tremoring of the extended arms (after latency of onset). There was evidence of slower movements and mild rigidity of the right arm>leg. On gait testing, he had reduced right arm swinging associated with asymmetric tremor of the right hand. His gait was slightly slower than normal with a narrower base. He had a reduced postural reflex and required more steps than expected for turns.

- What is the type(s) of tremor?
- What is the etiology of the tremor(s)?

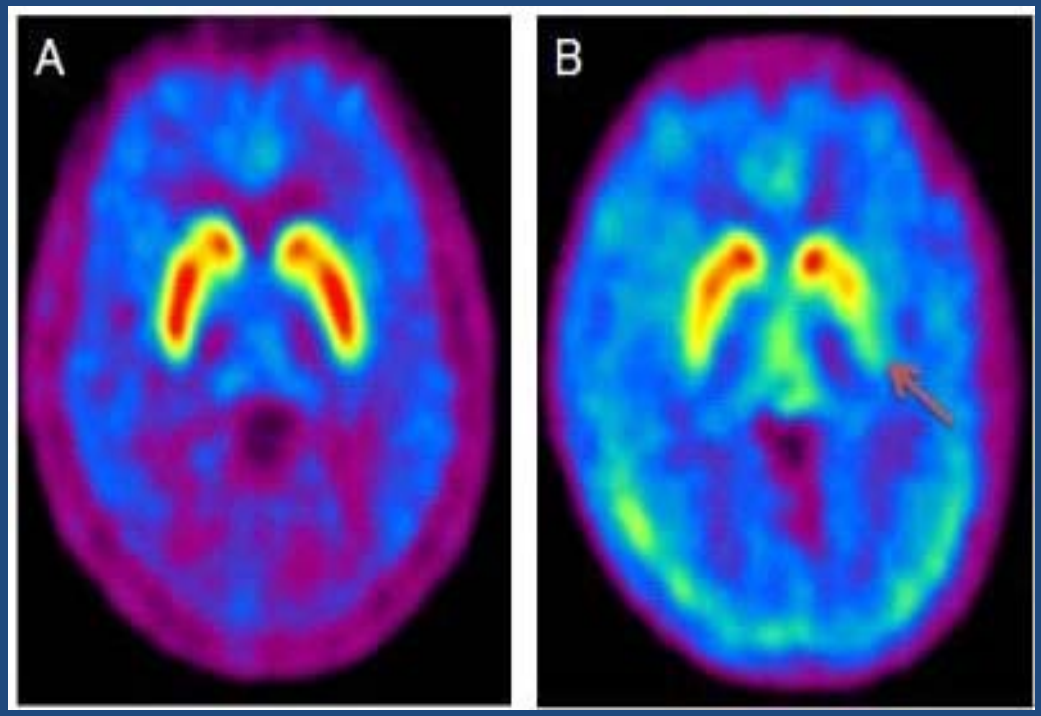
III. Distinguishing Essential Tremor from Parkinson's Disease

- Rest tremor does not usually occur in ET (though could be present in patients with more severe, chronic disease)
- However, action/postural tremor often coexists with rest tremor in patients with PD
  - Re-emergent tremor in PD has postural element (surfaces after a latency)
- Head/mouth tremor more common in ET. When present in PD, it typically occurs at rest (laying down, mouth relaxed)
- Over time, patients with ET could develop PD – ET is a known risk factor for PD.
- Dopamine transporter PET could help diagnostically
- Olfactory testing can be abnormal in both (therefore not diagnostically helpful).

Thenganatt et al., 2012

III. Reduced Dopamine Transporter in Parkinson's Disease

Normal and ET PD



Thenganatt et al., 2012

IV. Medical Treatment of Essential Tremor

- Goals of treatment are to reduce the amplitude of the tremor, improve function and/or reduce social embarrassment
- Treatment of mild tremor is not usually indicated
- 30-70% of patients have mild/moderate improvement (Louis et al., NEJM, 2011; Louis, 2016).
- Most medications that have been found to be effective were the result of serendipitous discovery
- Propranolol, primidone and Topiramate (>200mg/day) are first-line therapies
  - Per AAN practice guideline [Zesiewicz et al., 2005] and per Ferreira et al., 2019 evidence-based review.

Zesiewicz et al., 2005; Ferreira et al. 2019

IV. First-Line Treatment: Propranolol

- Peripheral b-adrenergic receptors probably mediate most of the effects of b-adrenergic blocking agents (Jefferson et al., 1979)
- Propranolol has been found to be effective in reducing the severity of tremor in placebo-controlled studies (45-75% reduction) at a minimum dose of 80-120mg/day (for example, Tolsa et al., 1975).
- Relative contraindications of propranolol include asthma, congestive heart failure, diabetes, AV block.
  - Doses as high as 240-36mg/day could be used; however, the elderly usually do not tolerate more than 100mg/day due to bradycardia
  - Other AE: bronchospasm, fatigue, LH, sexual dysfunction
- Non-selective beta antagonists, such as Propranolol, are more effective than b1 selective antagonists (Dietrichson et al., 1981).

IV. First-Line Treatment: Primidone

- Primidone is an antiepileptic medication that is metabolized to phenobarbital and phenylethylmalonamide.
- The parent compound mediates most of the effect against tremor
  - Although at least as effective as propranolol at 750mg/day, early tolerability is a limiting factor with primidone - nausea/vomiting and ataxia result in discontinuation in ~20%. Other AE: fatigue, dizziness
  - Pre-medicating with low dose PB may help (30mg bid for 3 days)
  - If tolerated, more patients prefer Primidone over Propranolol
- A typical starting dose is 50mg nightly and a very slow upward titration is recommended
- Combination therapy is reasonable: Propranolol and Primidone

Findley et al., *J Neurol Neurosurg Psychiatry* 1985

IV. First-Line Treatment: Topiramate

- Topiramate: Recent evidence-based review confirmed observations that Topiramate is helpful, but only using doses higher than 200mg/day.
  - AE: paresthesias, cognitive (word finding, concentration), weight loss, rare kidney stones

Ferreira et al. 2019

IV. Second-Line Therapies

- Gabapentin: In 2 of 3 trials GBP, at doses of 1200-3600mg, reduced tremor significantly (Ondo et al., 2000).
- Some benzodiazepines have been shown to be effective against tremor, however at the cost of sedation and potential dependence
- Calcium channel blockers have had mixed results: Some (nimodipine) appear to help, whereas others (nifedipine) may worsen tremor (Louis et al., NEJM, 2001).
- Overall, there is a level B recommendation (probably effective) for the use of gabapentin, alprazolam, atenolol, sotalol, and topiramate (Zesiewicz et al., 2005).

IV. Usual Approach in Clinic

- I start with Propranolol, aiming initially for 40-60mg bid and possibly as high as 240-360mg/day, unless there is a contraindication. I subsequently transition the patient to extended-release formulation.
- In case of no response to Propranolol, I next try Primidone, aiming gradually for 50mg bid. If tolerated, the dose could be increased to as high as 250mg bid-tid.
- I often use Topiramate as an alternative adjunctive agent (titrating initially up to 50mg bid over 4 weeks).

V. Non-medical Treatment of Essential Tremor

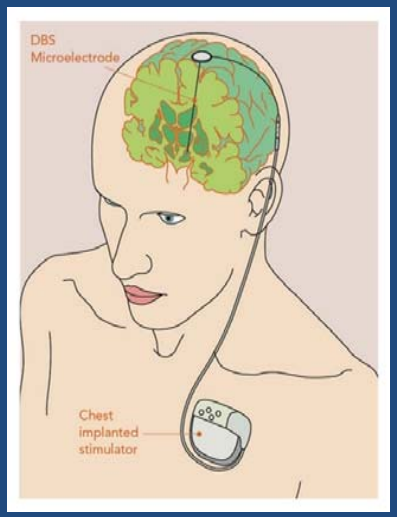
- Several surgical treatments have been used for the treatment of medically refractory, disabling limb ET:
  - Deep brain stimulation through an electrode implanted in the ventral intermediate nucleus (VIN) of the thalamus (contralateral to the more disabled arm)
  - Surgical or radiofrequency lesioning of VIN of the thalamus (thalamotomy)
  - Transcranial MRI-guided focused ultrasound thalamotomy (new targeted tissue thermal-ablation of the VIN)
  - Per the 2019 evidence-based review, all of these were considered "possibly useful"

Olanow et al. 2001; Ghanouni et al. 2015; Ferreira et al. 2019

V. Non-medical Treatment of Essential Tremor

- DBS delivers electrical stimulation via an implanted electrode to the VIN.

- The electrode is connected to a pulse generator, implanted in the left upper chest.



Olanow et al. *Neurology*. 2001

V. Comparing Surgical Options

- When compared, the two methods were found to be equally effective at reducing tremor (Schuurman et al., *NEJM*, 2000). However, thalamic stimulation was associated with fewer adverse effects (level B recommendation).
  - Thalamotomy is a fixed brain lesion, whereas with DBS there is the the potential to adjust stimulation parameters for further therapeutic gains
- Other notes: Bilateral stimulation is often needed, as stimulation on one side helps with the contralateral limb. Bilateral stimulation is also typically recommended for controlling head tremors, though there was insufficient evidence for the use of surgical interventions for voice and head tremors (per a 2019 evidence-based review of Ferreira et al).

Surgical Risks and Disadvantages

- General surgical risks associated with neurosurgery include: infection (increased from usual given use of device), bleeding, stroke.
- Neurological deficits: mainly altered sensation, speech and gait deficits. Careful risk/benefit assessment prior to surgery.
- Need to periodically replace battery with DBS - however, no need to replace the implanted electrodes and wires.

V. Botulinum Toxin

- Botulinum toxin A (Botox) is "possibly helpful", per the 2019 review.
- However, it is sometimes associated with transient hand weakness and the treatment needs to be repeated periodically.

VI. Treatment of Other Tremors

- Resting tremor, in the context of parkinsonism, often is challenging to treat:
  - Levodopa often improves bradykinesia and rigidity more than tremor
  - Treatment includes anti-cholinergic agents (including Amantadine up to 300mg/day, anti-muscarinic agents, especially Trihexyphenidate)
  - Benzodiazepines play a role
  - DBS for severe, refractory cases
- RT by definition does not occur while the limb is at function:
  - Other elements of PD – such as bradykinesia – are more impairing to the patient, and treatment is typically targeted at them.

Treatment of Medication-Induced Rest Tremor

- Important to identify reversible causes of parkinsonism, including neuroleptic agents:
  - Resting tremor is a common manifestation of “extra-pyramidal” symptoms related to neuroleptic use. Could appear identical to that of Idiopathic Parkinson’s Disease and could be accompanied by other “PD” signs.
  - Should eventually resolve with removal of the neuroleptic agent.
  - Symptomatic treatment may be necessary if it is not possible to remove the neuroleptic agent (for example due to uncontrolled psychosis).

Treatment of Medication-Induced A/P Tremor

- Not always feasible to discontinue the offending agent - for example, patient with difficult to control epilepsy who finally becomes controlled on Valproic Acid).

- Therefore, symptomatic medical treatment targeting the tremor may be implemented (typically with Propranolol). EPT does not respond as well to mainstream treatments.

Treatment of Dystonic Tremor

- Medications used to treat dystonia:
  - Trihexyphenidate up to 10mg/day
  - Baclofen up to 60mg/day
  - Benzodiazepines or beta blockers
- For dystonic neck tremor other options include:
  - Botulinum toxin injections
  - Selective denervation
  - DBS

Conclusions

- Careful history and examination are important to identify the type of tremor as a first step
- Action/postural tremor is one of several types of tremor, and essential tremor is the most frequent cause.
- The diagnosis of essential tremor necessitates excluding other etiologies of action/postural tremor
- Goals of treatment are to reduce tremor amplitude, improve function and/or reduce social embarrassment
- Propranolol and primidone remain the first-line therapies
- For disabling, medically refractory tremor, chronic unilateral thalamic stimulation or thalamotomy are effective surgical options

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Audience Polling Question #1

Which is the more disabling type of tremor?

1. Resting tremor
2. Action tremor

Audience Polling Question #2

The following are examples of pathological tremors except:

1. Physiological tremor
2. Resting tremor
3. Intention tremor
4. Essential tremor

Audience Polling Question #3

This type of tremor is typically seen in the setting of cerebellar disease:

1. Resting tremor
2. Essential tremor
3. Intention tremor
4. Physiological tremor

Audience Polling Question #4

The following tremors are progressive except:

1. Essential tremor
2. Physiological tremor
3. Tremors associated with Parkinson's disease (rest, action)
4. Tremor associated with idiopathic dystonia

Audience Polling Question #5

The goal of treatment for essential tremor is to:

1. Reduce the amplitude of the tremor
2. Reduce functional impairment
3. Reduce the patient's social embarrassment
4. 2 and 3
5. All of the above

Audience Polling Question #6

The following medication(s) are first-line treatments for essential tremor:

1. Propranolol
2. Primidone
3. Gabapentin
4. 1 and 2
5. 2 and 3

Audience Polling Question #7

Selective beta-1 adrenergic blockers are more effective than non-selective agents for the treatment of essential tremor:

1. True
2. False

Audience Polling Question #8

A toxic reaction, including GI and neurological symptoms, is commonly encountered with early primidone therapy:

1. True
2. False

Audience Polling Question #9

Thalamic stimulation results in fewer adverse effects compared to thalamatomy:

1. True
2. False