

Case Illustration: Essential Tremor (ET)

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Patient History and Exam:

A 66yo, left-handed woman presents with complaints of hand and arm tremor. She does not have any tremor while at rest, but the tremor worsens significantly when trying to perform tasks with her hands. In particular, she has trouble eating and holding utensils, as well as putting on makeup. The embarrassment from the tremor keeps her from being as social as she once was. Alcohol reduces the tremor and sometimes she will have a glass of wine before an event so she feels more socially acceptable.

She states that she first noticed the tremor in her left hand while in her early thirties. The tremor has since progressed to both upper extremities, in addition to a small head tremor. She denies any slowness of movements, stiffness, memory, balance, or other symptoms. Her family history is notable for two paternal uncles, and a daughter who also have similar tremors. Her daughter was diagnosed at the age of 16.

On examination, only a very mild head tremor is noted while she is seated with her hands in her lap. A 10 Hz tremor becomes apparent as she raises her arms into sustentation. The tremor amplitude increases when she attempts to perform a task or take a drink of water. She cannot consistently keep her hand down on a sheet of paper to draw an Archimedes spiral or write her name. No other abnormalities are found on exam.

Teaching points:

- The prevalence of ET is estimated from 0.4-6%, the incidence increasing with age.
- The distribution is bimodal, with peaks in early adulthood and in those >60 yo.
- Approximately half of patients have a family history of ET
- Features that support diagnosis of ET:
 - Alcohol suppresses the tremor
 - Tremor is predominately postural and action
 - Frequency of 4-12 Hz and regular
 - Additional presence of head and/or voice tremor
 - Normal gait
 - Lack of bradykinesia, rigidity, or other neurologic deficits
- Other causes of tremor must be ruled out, especially medications

Treatment:

Her tremor was manageable for many years with medication. Specifically, she had been well-controlled with propranolol, however she began having low blood pressure with increasing doses. She has also tried topiramate and clonazepam without sufficient benefit. She is currently taking primidone, which has required increasingly escalating doses to control her tremor. Despite this, her tremor greatly interferes with daily activities. She now presents to discuss other treatment options.

Medication summary:

- Propranolol is the only medication with FDA indication for tremor treatment
- Level A evidence: propranolol, primidone
- Level B evidence: alprazolam, atenolol, gabapentin, sotalol, topiramate
- Level C evidence: clonazepam, nadolol, nimodipine

Surgical Treatment:

You discuss the currently available interventions:

Deep Brain Stimulation (DBS)

- A small cylindrical electrode is placed using a stereotactic frame into the ventral intermediate (VIM) thalamus
- Testing is typically performed during surgery to confirm electrode location and suppression of tremor
- The electrode is connected to an implanted pulse generator, which allows for programming and optimization of high-frequency stimulation for tremor control.
- Reversible
- Outcomes: 60-90% improvement in tremor control of contralateral limb
- Bilateral stimulation can be performed to allow for bilateral tremor control
- Stimulation side effects include dysarthria and decreased fluency, paresthesia, imbalance/disequilibrium – typically can be managed by adjusting stimulation parameters
- Dysarthria and disequilibrium more common with bilateral stimulation
- Risks include stroke, hemorrhage, infection, hardware malfunction or breakage, seizures
- Data limited in support of efficacy in voice and head tremor control, though bilateral may be more effective than unilateral
- Patients can develop tolerance to stimulation and reduced tremor control over time
- Not indicated for patients with high surgical risk of infection, wound breakdown, bleeding, or those who cannot cooperate with intra-procedural testing

Thalamotomy

- Creation of a permanent lesion in the VIM nucleus of the thalamus using stereotactic techniques and intra-operative, electrophysiologic testing
- No implanted hardware remains
- Tremor resolves in 80-90% of patients
- Similar risks and side effects as DBS, though higher rate (~15%) of permanent deficits

- Due to the high rate (30-60%) of side effects, specifically dysarthria, bilateral thalamotomy is not recommended
- Not recommended for patients with high bleeding risk or patients who cannot cooperate with intra-procedural testing

Gamma Knife™

- Non-invasive approach to thalamotomy, using stereotactic frame for localization
- No physiologic control of lesion
- Benefit delayed, developing over weeks to months
- Side effects (dysarthria, contralateral arm or leg numbness) also delayed
- Other technologies for stereotactic radiosurgery have been used with similar effects
- Outcomes – 75-92% tremor-free at one year
- Not recommended for patients who require bilateral tremor control

High Frequency Focused Ultrasound

- Non-invasive approach to thalamotomy, using MRI guidance for localization
- Requires complete head shave, limited availability due to few number of centers
- Immediate benefit
- Intra-procedural testing allows for some physiologic control
- Limited outcome data available, initial studies indicate 80-90% tremor improvement
- Not recommended for patients who require bilateral tremor control, high risk of bleeding, or who cannot cooperate with intra-procedural testing

Clinical Decision:

The patient did not have any contraindications to surgery or device implantation and desired bilateral control of her tremors. She elected to undergo bilateral deep brain stimulation implantation with 85% reduction in her tremor.

Summary:

Several treatments are available for Essential Tremor, including invasive and non-invasive interventions for medically refractory patients. Deep Brain Stimulation is the most widely used surgical intervention due to its reversibility and the ability to treat bilateral tremor. Gamma Knife and Focused Ultrasound provide less invasive options for patients not appropriate for DBS, though bilateral treatment is contraindicated and less long-term data is available.

References:

- Akbostanci MC, Slavin KV, Burchiel KJ. Stereotactic ventral intermedial thalamotomy for the treatment of essential tremor: results of a series of 37 patients (1999) *Stereotact Funct Neurosurg* 72: 174–177.
- Barbe MT, Liebhart L, Runge M, et al. Deep brain stimulation in the nucleus ventralis intermedius in patients with essential tremor: habituation of tremor suppression (2011) *J Neurol* 258: 434-439.
- Boockvar JA, Telfeian A, Baltuch GH, et al. Long-term deep brain stimulation in a patient with essential tremor: clinical response and postmortem correlation with stimulator termination sites in ventral thalamus. Case report (2000) *J Neurosurg* 93 :140–144.
- Carpenter MA, Pahwa R, Miyawaki KL, et al. Reduction in voice tremor under thalamic stimulation (1998) *Neurology* 50: 796–798.
- Elias WJ1, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor (2013) *N Engl J Med* 369: 640-648.
- Elias WJ and Shah BB. Tremor (2014) *JAMA* 311: 948-954.
- Hariz MI, Shamsgovara P, Johansson F, et al. Tolerance and tremor rebound following long-term chronic thalamic stimulation for Parkinsonian and essential tremor (1999) *Stereotact Funct Neurosurg* 72: 208-218.
- Hubble JP, Busenbark KL, Wilkinson S, et al. Deep brain stimulation for essential tremor (1996) *Neurology* 46: 1150–1153.
- Koller W, Pahwa R, Busenbark K, et al. High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor (1997) *Ann Neurol* 42: 292–299.
- Lipsman N1, Schwartz ML, Huang Y, et al. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study (2013) *Lancet Neurol* 12: 462-468.
- Nagaseki Y, Shibasaki T, Hirai T, et al. Long-term follow-up results of selective VIM-thalamotomy (1986) *J Neurosurg* 65: 296–302.
- Niranjan A, Kondziolka D, Baser S, et al. Functional outcomes after gamma knife thalamotomy for essential tremor and MS-related tremor (2000) *Neurology* 55: 443–446.
- Pahwa R, Lyons KL, Wilkinson SB, et al. Bilateral thalamic stimulation for the treatment of essential tremor (1997) *Neurology* 53: 1447–1450.
- Putzke JD1, Uitti RJ, Obwegeser AA, et al. Bilateral thalamic deep brain stimulation: midline tremor control (2005) *J Neurol Neurosurg Psychiatry* 76: 684-690.
- Taha JM, Janszen MA, Favre J. Thalamic deep brain stimulation for the treatment of head, voice, and bilateral limb tremor (1999) *J Neurosurg* 91: 68–72.
- Young RF, Jacques S, Mark R, et al. Gamma knife thalamotomy for treatment of tremor: long-term results (2000) *J Neurosurg* 93: 128–135.

Zesiewicz TA, Elble RJ, Louis ED, et al. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology (2005) *Neurology* 64: 2008-2020.

Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: Treatment of essential tremor, Report of the Quality Standards Subcommittee of the American Academy of Neurology (2011) *Neurology* 77: 1752-1755.

Zirh A, Reich SG, Dougherty PM, et al. Stereotactic thalamotomy in the treatment of essential tremor of the upper extremity: reassessment including a blinded measure of outcome (1999) *J Neurol Neurosurg Psychiatry* 66: 772–775.