No, it is not Parkinson’s disease!

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Université de Montréal
tremor in Parkinson

• pill rolling: involve the thumb and the index, can also be wrist flexion/extension, supination/pronation of forearm

• can involve legs, mandible
  • rarely the head

• at rest: goes away with action

• can appear or be increased by distraction

• re-emergent tremor

• 60% of patients with PD have tremor

• patients can also have portural/action tremors of same or different frequencies than the resting tremor
rest tremor - DDX

iatrogenic

- D2 blockers
- Ca channel blockers
- lithium
- valproate
- amiodarone

• vascular parkinsonism
• SCA 2 and 3
• RT can be present in association with other types of tremors (essential, dystonic, Holmes)
tremors in SWEDD’s

- SWEDD: Scan Without Evidence of Dopaminergic Deficit
- 2 yr f/u in 34 patients with tremor
- clinical evaluation at 24 moths, scan on 12 patients with still undetermined dx

la différence est claire!
What is the link between ET and PD?

• 46% of patients with PD have postural tremor
  • Gigante et al Eur J Neurol 2014

• prevalence of ET before the Dx of PD is the same as in the general population
  • Rana et al Int J Nsci 2014

• no alpha-synucleine variant (20 SNP’s on 661 ET vs 1216 in 427 PD)

• differentiation between PD and ET with Tension Diffusion imaging
treatment of tremor in PD

- dopaminergic agents
- anticholinergic agents
- thalamic surgeries
treatment of rest tremor other than PD

- stop causative agents

- tardive:
  - tetrabenazine
  - clozapine?
rythmic oscillation of a body part

• which body part?
• what frequency?
• what context?
body part

head
- dystonia
- ET

mandible
- Parkinson
- dystonia
- hereditary geniospasm

palate
- essential
- secondary (cerebellar lesion)
- GFAP mutation (associate to Alexander disease)

lower limbs
- orthostatic tremor
- Parkinson
frequency

low frequency: < 4 Hz

• Holmes tremor

mid frequency: 4 to 7 Hz

• rest tremor of PD

high frequency: > 7 Hz

• ET

• orthostatic tremor (13-18 Hz)
**context of tremor**

**Table 1 | Classification of tremors according to moment of occurrence**

<table>
<thead>
<tr>
<th>Moment of occurrence</th>
<th>Features</th>
<th>Example of underlying disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. At rest</td>
<td>Best judged in a body part that is fully supported against gravity</td>
<td>Parkinson disease</td>
</tr>
<tr>
<td>B. With action</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postural</td>
<td>Occurs in body part that assumes a posture against gravity</td>
<td>Physiological; enhanced physiological (stress, endocrine disorders or intoxications); essential tremor</td>
</tr>
<tr>
<td>Kinetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td>Occurs during entire movement trajectory</td>
<td>Essential tremor</td>
</tr>
<tr>
<td>Intention</td>
<td>Progressively increases towards intended target</td>
<td>Cerebellar ataxia</td>
</tr>
<tr>
<td>Task specific</td>
<td>Occurs only during specific activities</td>
<td>Dystonic writing tremor</td>
</tr>
<tr>
<td>Isometric</td>
<td>Occurs during voluntary muscle contractions against a stationary resistance</td>
<td>Physiological; associated with other types of tremor</td>
</tr>
<tr>
<td>C. Combinations</td>
<td>Various</td>
<td>Severe essential tremor; atypical parkinsonism; dystonic tremor; rubral (Holmes) tremor</td>
</tr>
</tbody>
</table>

The above classification was proposed by a Consensus Statement of the Movement Disorder Society.¹⁷
essential tremor

- essential = essence of the syndrome, ≠ nécessaire
- benign essential tremor = not associated to a deadly disease, ≠ no handicap
- 1% of the population de > 65 yrs
- 27% of patients with ET will seek medical attention
- progression very slow
- familial history suggestive of a dominant inheritance
- usually upper limbs (95%), but can also involve the head (30%), the voice (20%), the mandible (10%), the tongue (20%), the trunk (5%) and the lower limbs (10%)
- relatively symmetrical
- postural and action
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of diagnostic criteria for essential tremor according to TRIG, Movement Disorders Society, and Bain et al.(^5,6)</th>
</tr>
</thead>
</table>
| **Core criteria\(^5\)** | 1. Bilateral postural and kinetic tremor of the hands and forearms (but not rest tremor) (TRIG, MDS, Bain et al.)  
2. Absence of other neurologic signs (TRIG, Bain et al.)  
3. May have isolated head tremor with no signs of dystonia (MDS, Bain et al.) |
| **Duration and level of certainty\(^6\)** | 1. Definite ET: duration >5 years + comprehensive exclusion of other causes + no stepwise deterioration (TRIG)  
2. Probable ET: duration >3 years + same criteria as definite ET (TRIG)  
3. Possible ET: no duration criterion + type I: some other neurologic symptoms allowed; type II: monosymptomatic or isolated tremors of uncertain relation to essential tremor (TRIG) |
| **Secondary criteria\(^5\)** | 1. Positive family history (present in 30%-60% of patients) (Bain et al.)  
2. Beneficial alcohol response (present in 50%-75% of patients) (Bain et al.) |

Abbreviations: ET = essential tremor; MDS = Movement Disorders Society; TRIG = Tremor Investigation Group.
## ET: dx criteria

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria:</strong></td>
<td><strong>Inclusion criteria:</strong></td>
</tr>
<tr>
<td>1. Bilateral postural tremor, with or without kinetic tremor, in the hands that is visible and persistent</td>
<td>1. Bilateral, largely symmetric postural or kinetic tremor of the hands that is visible and persistent</td>
</tr>
<tr>
<td>2. Duration longer than 5 years</td>
<td>2. Additional or isolated head tremor in the absence of abnormal posturing</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong></td>
<td><strong>Exclusion criteria:</strong></td>
</tr>
<tr>
<td>1. Other abnormal neurologic signs (with the exception of the presence of tremor and Froment’s sign. The full neurologic examination should be normal for age)</td>
<td>1. Other abnormal neurologic signs, especially dystonia</td>
</tr>
<tr>
<td>2. Presence of known causes of enhanced physiologic tremor</td>
<td>2. The presence of known causes of enhanced physiologic tremor, including current or recent exposure to tremorogenic drugs or the presence of a drug withdrawal state</td>
</tr>
<tr>
<td>3. Concurrent or recent exposure to tremorogenic drugs or the presence of a drug withdrawal state</td>
<td>3. Historic or clinical evidence of psychogenic tremor</td>
</tr>
<tr>
<td>4. Direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor</td>
<td>4. Convincing evidence of sudden onset or evidence of stepwise deterioration</td>
</tr>
<tr>
<td>5. Historic or clinical evidence of psychogenic origins of tremor</td>
<td>5. Primary orthostatic tremor</td>
</tr>
<tr>
<td>6. Convincing evidence of sudden onset or evidence of stepwise deterioration</td>
<td>6. Isolated voice tremor</td>
</tr>
<tr>
<td>7. Isolated position-specific or task-specific tremors, including occupational tremors and primary writing tremor</td>
<td>7. Isolated tongue or chin tremor</td>
</tr>
<tr>
<td>8. Isolated leg tremor</td>
<td>9. Isolated leg tremor</td>
</tr>
</tbody>
</table>
tremor in ET, an isolated symptom? ATTENTION: controversial

complex syndrome

• clinical cerebellar symptoms
  • intention tremor
  • dysmetria and overshoot
  • difficulty with the tandem
  • abnormalities of the vestibulo-ocular system

• diminished survival (littérature variable)
ET
the non-motor syndrom

ET (vs normal population)

• hyposmia 4.5% (idem)
• constipation 21.7% (idem)
• RBD 43.5% (vs 0.5%)
• depression 17.6 - 21.7% (vs 5%)
• more MCI (69.2%) and higher rate of conversion form normal to MCI 25% within 2 yrs, but conversion to dementia (8.4% within 2 yrs, idem)
• anxiety (25%)
ET, a degenerative disease of an abnormal cerebello-thalamique oscillation? ATTENTION: controversial pathologic syndrome

- Lewy bodies, Torpedoe cells, gliosis of Bermann

- no difference between TE, PD forme tremblante, and normal controls for the loss of Purknjie neurons
  - Rajput et Rajput, Park and Rel Dis 2011, Shill, Adler & Beach, Park and Rel Dis 2012, Rajput et al Park and Rel Dis 2012
isolated tremor of the head

- ET or dystonic tremor?
- dystonic tremor = thickening of sensori-motor and of primary motor cortex
- ET= atrophy of anterior cerebellar cortex
postural tremor: DDX

- physiologic tremor
- toxic (mercury, e.g.)
- metabolic
- fragile X
- neuropathy
- Parkinson

iatrogenic
- valproate
- T4
- lithium
- tricyclic antidepressants

stimulating agents
- adrenergic agonists (salbutamol, e.g.)
- cocain
- cafein
- amphetamine
- nicotine
AAN guidelines 2011

- propranolol, primidone (Level A, established as effective);
- alprazolam, atenolol, gabapentin (monotherapy), sotalol, topiramate (Level B, probably effective)
- nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation, thalamotomy (Level C, possibly effective)
- gamma knife thalamotomy (Level U, insufficient evidence)

1) levetiracetam, 3,4-diaminopyridine should not be considered (Level B)
2) flunarizine (Sibelium) may not be considered (Level C)
3) pregabalin, zonisamide (Zonegan/Tremode), or clozapine (Level U, insufficient evidence)
# treatments for ET

## Table 1 Recommended drugs for essential tremor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean or median effective daily dosage</th>
<th>Estimated percentage improvement in tremor amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>40–240 (320) mg/d</td>
<td>32–75</td>
</tr>
<tr>
<td>Primidone</td>
<td>&lt;62.5 –750.0 mg/d</td>
<td>42–76</td>
</tr>
<tr>
<td>Topiramate</td>
<td>100–333 mg/d</td>
<td>30–41</td>
</tr>
</tbody>
</table>

## Table 2 Drugs for essential tremor with probable or weak efficacy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean or median effective daily dosage</th>
<th>Estimated percentage improvement in tremor amplitude</th>
<th>Percentage improvement by accelerometry [ref.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>50–100 mg/d</td>
<td>24–38 [21, 22]</td>
<td>37 [23]</td>
</tr>
<tr>
<td>Sotalol</td>
<td>80–240 mg/d</td>
<td>29–51 [21, 22]</td>
<td>–</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1200–1800 mg/d</td>
<td>39 [24]</td>
<td>77</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.75–1.5 mg/d</td>
<td>48–60 [25, 26]</td>
<td>–</td>
</tr>
</tbody>
</table>

## Table 3 Drugs for essential tremor with uncertain efficacy (likely not efficacious)

<table>
<thead>
<tr>
<th>Level C possibly effective (daily dosage of the respective studies) [ref.]</th>
<th>Agents with recommendations against use</th>
<th>Inadequate evidence to confirm or exclude efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam (0.5–4.0 mg) [27]</td>
<td>Acetazolamide/methazolamide</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Clorazapate (18–75 mg) [28]</td>
<td>Amantadine</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>Flunarizine (10 mg) [29]</td>
<td>Carisbamate</td>
<td>Tiagabine</td>
</tr>
<tr>
<td>Nadolol (120–240 mg) [30]</td>
<td>Isoniazid</td>
<td>Sodium oxybate</td>
</tr>
<tr>
<td>Nimodipine (120 mg) [31]</td>
<td>Levetiracetam</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Botulinum toxin (depending on injected muscles)</td>
<td>Pindolol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trazodone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3,4-Diaminopyridine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
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<tr>
<td></td>
<td>Nifedipine</td>
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<tr>
<td></td>
<td>Verapamil</td>
<td></td>
</tr>
</tbody>
</table>
ET: treatment for the upper limbs

- botulinum toxin
  - objective improvement (accélérometer)
  - no subjective improvement
  - 30-70% weakness

- thalamotomy or thalamic stimulation
  - target = dentato-rubro-thalamic tract
  - stimulation: détérioration 73% within 5 yrs

- STN or zona incerta stimulation

- radio surgery (gamma knife)

- MRI guided ultrasound surgery
dystonic tremor

• dystonic tremor: tremor of a limb that is affected by dystonia

• tremor associated to dystonia: tremor in a limb that is not affected by dystonia, but in a patient with dystonia
  • irregular amplitude and variable («jerky») frequency
  • position-specific, specific to a task (nul position)
  • improved by a «geste antagoniste»
  • worse in movements that go against the direction of the torsion of dystonia

• controversial: tremor with characteristics of dystonic tremor, but in a patient without dystonia
• **A, B, C, D = ET**

• **E = DT**

• **ET = one axis**

• **TD = no predominant axis**
dystonic tremor

• 17% of patients with dystonia
• mainly in cervical dysotnia
• 10% = DT and 5% TAD, 2% = DT and TAD
• manifestations of DT and of TAD are very similar

55.4% of patients with dystonia (473)
• 41% head tremor
• 30% tremor of an upper limb
• very rare: sup or middle part of the face
• mandible (open-close or latero-lateral)
• 21% combination head and upper limb
  • postural 100%
  • action 73.6%
  • rest 40.7%
DT: treatment algorithm
Fasano et al JNNP 2014

Primary writing tremor
- Gpi+Vim DBS (in case of both tremor and dystonic postures)
- Bilateral procedures (in case of head/axial tremor)

Tremor of head/jaw/vocal cord
- BoNT

BoNT (sites not adequately improved)

Arm tremor \pm tremor of head/jaw/vocal cord
- Anticholinergic \pm tetrabenazine \pm clonazepam (beta-blockers/primidone)

Unilateral DBS
- Vim (PWT or mainly tremor)
- Gpi (if also dystonic postures are present)

Unsatisfactory effects
treatment of dystonic tremor

- mild to moderate efficacy
  - anticholinergics
  - tetrabenazine
  - clonazepam
  - beta-blockers
  - primidone

- levodopa only efficacious in DRD

- botulinum toxin mainly for hand and voice tremor

- lesioning surgeries
  - thalamotomy
  - focused ultrasound thalamotomy
  - radiosurgery (gamma-knife, cyber-knife)

- deep brain stimulation
  - thalamus
  - globus pallidus
  - sub-thalamic nucleus
  - combination of targets

Fasano et al JNNP 2014
ET or DT?

new nomenclature: primary postural tremors

- DT si sometimes so rhythmic that it is impossible to differentiate from ET
- tremor may be the only manifestation of dystonia (dystonia gene associated tremor) Deuschl, Bain, Brin. Mov Dis 1998;13:2-23
- ET is a syndrome that is common to many diseases
- mild dystonia often not diagnosed in cases of ET
- the specificity of geste antagonistes, null position, irregularity, task-specificity, overflow is unknown

electrophysiology
- not specific (TCMCS and H-reflex)

likely one of the principal reasons why discovery of ET genes remain elusive

Defining Dystonic Tremor
Rodger J. Elble* Current Neuropharmacology, 2013, 11, 48-52
primary writing tremor

- the most common task specific tremor
  - primary bowing tremor has been described
  - good response to botulinum toxin injections and thalmaic surgeries

**differences from ET**

- More often in people from Africa, in men, older (47 vs 39 years)
- less likely to have a familial history
- less responsive to medications and to alcohol
- evolution to addition of other task-specific tremor, resting or mixed tremor, but not to postural tremor

*Citation: Lee A, Chadde M, Altenmüller E, et al. Characteristics of task-specific tremor in string instrument players. Tremor Other Hyperkinet Mov. 2014; 4. doi: 10.7916/D86Q1V9W*
orthostatic tremor

- 4.5 to 40 years before obtaining the dx
- 30% unsteadiness
- progressive or stable
- improvement with alcohol, bent posture, walking, sitting
- no familial hx
- treatment =
  - clonazepam 1mg die (0.25 to 3.5)
  - gabapentin
- pure or associated to other movement disorders (ot-plus)
  - 30%
- PD, LBD, vascular parkinsonism, PSP, primary FOG, RLS, ET, multifocal action tremor, focal dystonia, oro-facial dyskinesia
FXTAS

- tremor of FXTAS
- essential-like 35%
- small amplitude
- cerebellar 29%
- resting 12%
- unilateral

**Fig. 2.** FXTAS pathology. (A) Eosinophilic neuronal intranuclear inclusions. (B) Intraneuronal inclusions stained with antiubiquitin antibodies.

**Fig. 3.** Clinical and pathogenic effects of expanded CGG repeats in the FMR1 gene. The repeat expansion ranges are located in the left portion of the figure. In individuals with the premutation, there is an increase in FMR1 mRNA, which leads to inclusion formation and FXTAS. In individuals with a full mutation, the promoter and CGG repeat is methylated, the gene is silenced, and fragile X syndrome occurs. (From Hagerman PJ, Hagerman RJ. Fragile X-associated tremor/ataxia syndrome—an older face of the fragile X gene. Nat Clin Pract Neurol 2007;3(2):107–12; with permission.)
Holmes tremor

- rest and intention
- 4-5 Hz
- can be impossible differentiate from a termor due to a lesion of the dorso-lateral thalamus (usually associated to dystonia)

**treatment**

- levodopa high doses
- trihexyphenidyl ad 12 mg
- clonazepam ad 4 mg
- clozapine ad 75 mg
- levitiracetam
- thalamic stimulation or two targets (variable)
tremor associated to a neuropathy

- treatment of the neuropathy
- propranolol
- pregabalin
- thalamic stimulation
mandibular tremor

- ET
- iatrogenic
- Parkinson
- DT
- tremor associated to dystonia
- tremor associated to dental work
funcitonal (psychogenic) tremor

- 55% of functional movement disorders
- remission 20-60%
- treatment by a multidisciplinary team
  - psychotherapy
  - physiotherapy
  - medical PRN
- acute onset
- highly variable
- coherence: tremor of different segments with same rythm
- «inconsistence»
- increased amplitude with weigh
- distractibility and «entrainment»
- suggestibility
- inability to double-task
- pause of tremor during a rapid action
- spontaneous remissions
- other symptoms (false neurological signs, hypersensitvity to stimuli [startle])
functional tremor

no difference in severity, but difference in variability inbetween the 10 spirals

Increased variability in spiral drawing in patients with functional (psychogenic) tremor
Christopher W. Hess, Annie W. Hsu, Qiping Yu, Robert Ortega, Seth L. Pullman

Fig. 2. Representative spiral drawings from a participant in each of the subject groups. Ten spirals are drawn for each participant. The spiral severity and tightness indices were determined for each spiral and the range between the 25th and 75th percentile of spiral tightness (25–75th tightness range) was calculated across 10 spirals. Note that while both tremor groups reveal severely abnormal spirals, the variability between spirals is greater in the middle functional tremor set.
tremors in MS

• postural/action/intention

• medications usually useless

botulinum toxin

• significant improvement 6 and 12 weeks post injection

• weakness 42%

thalamotomy or thalamic stimulation

• remains the best treatment
tremor in MSA-P

- 80% of patients
- rest (33%)/postural (50%)/action (20%)/intention (20%)
- symmetrical or asymmetrical
- irregular «jerky» or myoclonic (cortical minipolymyoclonus)
  - stimulus-sensitive myoclonus in the upper limbs (30%)
  - supportive for a Dx of MSA
- pill rolling < 10%
- head, tongue, chin, lips, legs: rare
  - supportive for a Dx of PD
- LD, amantadine, propranolol, clonazepam, but not anticholinergics
tremor in PSP

- PSP-P
- not described in the literature
- cases of ET have been described to evolve to PSP
  - 11 cases have evolved within 5-49 years to parkinsonism or dementia
  - none were diagnosed with PSP
  - all had a pathological dx of PSP