

International Parkinson and
Movement Disorder Society
European Section



5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 6

**EAN/MDS-ES: Movement disorders for general neurologists
(Level 2)**

Diagnosis and Therapy of essential tremor

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Movement Disorder sessions at the
5th Congress of the European Academy of Neurology are done in
collaboration between MDS-ES and the EAN.



Diagnosis and Therapy of Essential Tremor

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Disclosures

I have no conflicts of interest related to the present research
 PI in trials with Abbvie, Acadia, Axon

RESEARCH ARTICLE

Consensus Statement on the Classification of Tremors, From the Task Force on Tremor of the International Parkinson and Movement Disorder Society

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 Claudia M. Testa, MD, PhD,⁹ Guenther Deuschl, MD, PhD ^{7*} and
 the Tremor Task Force of the International Parkinson and Movement Disorder Society[†]

- **Axis 1: phenomenology**
 - Essential tremor (ET) is a syndrome
 - ET plus – ET associated with other symptoms / signs
- **Axis 2: etiology**

Genome-wide association study in essential tremor identifies three new loci

Stefanie H. Müller,^{1,*} Simon L. Girard,^{2,3,*} Franziska Hopfner,^{1,*} Nancy D. Merner,^{3,4} Cynthia V. Bourassa,⁵ Delia Lorenz,⁵ Lorraine N. Clark,⁶ Lukas Tittmann,⁷ Alexandra I. Soto-Ortolaza,⁸ Stephan Klebe,^{9,10} Mark Hallett,¹¹ Susanne A. Schneider,^{1,12} Colin A. Hodgkinson,¹³ Wolfgang Lieb,⁷ Zbigniew K. Wszolek,⁸ Manuela Pendziwiat,¹⁴ Oswaldo Lorenzo-Betancor,^{15,16} Werner Poewe,¹⁷ Sara Ortega-Cubero,^{15,16} Klaus Seppi,¹⁷ Alex Rajput,¹⁸ Anna Husli,¹⁷ Ali H. Rajput,¹⁸ Daniela Berg,¹ Patrick A. Dion,³ Isabel Wurster,¹⁹ Joshua M. Shulman,^{20,21} Karin Srulijes,¹⁹ Dietrich Haubenberger,¹¹ Pau Pastor,^{15,16} Carles Vilariño-Guell,²² Ronald B. Postuma,^{3,23} Geneviève Bernard,^{1,24} Karl-Heinz Ladwig,^{25,26} Nicolas Dupré,²⁷ Joseph Jankovic,^{3,27} Konstantin Strauch,^{28,29} Michel Panisset,³⁰ Juliane Winkelmann,^{31,32} Claudia M. Testa,³³ Eva Reischl,^{25,34} Kirsten E. Zeuner,¹ Owen A. Ross,⁸ Thomas Arzberger,^{25,34} Sylvain Chouinard,³⁰ Günther Deuschl,¹ Elan D. Louis,³⁷ Gregor Kuhlenbäumer¹ and Guy A. Rouleau³

Downloaded from http://brain.oup.com/

- **3 loci related to molecules associated with various functions (STK32B, PPARGC1A, CTNNA3)**
- **expression of STK32B was increased in the cerebellar cortex of ET patients**
- **replication of SNP of previous G-W association studies (SLC1A2, LINGO1) did not confirm their association with ET**



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What questions does a general neurologist ask for a patient presenting with tremor

What questions does EVERY neurologist ask for a patient presenting with tremor

1. Is it tremor?
2. What kind of tremor is it?
3. Are there any associated symptoms and signs?
4. What is important in patient history?
5. Which exam/laboratory can help the diagnosis?
6. What is the right treatment?

Is it tremor?

„involuntary, rhythmic, oscillatory movement of a body part“

Deuschl et al. 1998, Bhatia et al. 2018

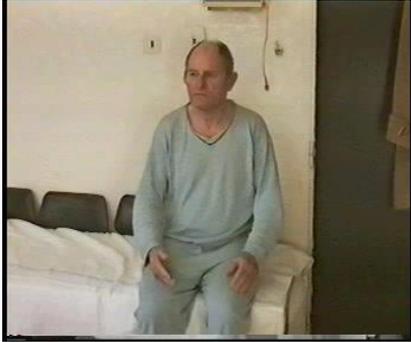


tremor

What kind of tremor is it?

What are the main tremor characteristics

(**activation conditions**, body distribution, frequency + amplitude)



resting



action postural



action kinetic

What kind of tremor is it?

What are the main tremor characteristics

(activation conditions, **body distribution**, frequency + amplitude)

- resting
- postural
- kinetic
- upper limbs
- head
- other

What kind of tremor is it?

What are the main tremor characteristics

(activation conditions, body distribution, **frequency + amplitude**)

- | | | |
|------------|---------------|----------------|
| • resting | • upper limbs | > 12 Hz (fast) |
| • postural | • head | 4 - 12 Hz |
| • kinetic | • other | < 4 Hz (slow) |

Are there any associated symptoms and signs?

- dystonia
- resting component to a postural tremor
- bradykinesia and/or rigidity
- disorders of stance and gait
- cognitive dysfunction
- ...

What is important in patient history?

- age at onset
- initial symptom / first body part affected by tremor
- development over time
- family history

Which laboratory tests can help the diagnosis?

<i>test</i>	<i>type of patient/symptoms</i>
specific maneuvers	suspicion of functional movement disorder (inconsistency, incongruency of signs, etc.)
MRI	every patient
DaTSCAN SPECT	resting tremor, tremor associated with bradykinesia/rigidity
urinary copper/24 h	patients < 45 (to exclude Wilson's disease)
electrophysiology	orthostatic tremor

Diagnosis and Therapy of Essential Tremor (ET)

Why it is important?

- the most prevalent form of pathological tremor, the most frequent movement disorder
 - 1-4% of population (20% above 65 yrs)
 - 20 times more frequent than Parkinson's disease
- chronic, slowly progressive course
- in 50-70% patients familial occurrence suggestive of autosomal dominant inheritance



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Even though „benign“, ET causes significant functional impairment

- handwriting and signature
- eating and drinking



- hand movements (fine crafts, dressing, ...)
- speech
- social embarrassment



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Diagnosis of Essential Tremor (ET)

Tremor characteristics in ET

- **type of tremor**
 - action postural with or without kinetic component
- **body distribution**
 - upper limbs, bilateral
 - with or without head, voice, or lower limbs tremor
- **associated symptoms/signs**
 - none in ET
 - present in „ET plus“
- **history**
 - early or late onset

Diagnosis of Essential Tremor (ET)

Diagnostic criteria

definition

- 1) isolated syndrome of bilateral upper limb action tremor
- 2) at least 3 years' duration
- 3) with or without tremor in other locations (e.g., head, voice, or lower limbs)
- 4) absence of other neurological signs, such as dystonia, ataxia, or parkinsonism.

exclusion criteria

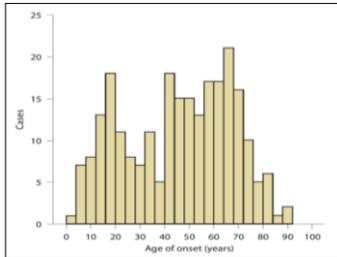
- isolated focal tremors (voice, head)
- orthostatic tremor with a frequency >12 Hz
- task- and position-specific tremors
- sudden onset and step-wise deterioration

Bhatia et al. 2018

Diagnosis of Essential Tremor (ET)

What is important in patient history?

- **age at onset**



Louis ED, Dogu O (2007)

- increased incidence > 60 yrs
- bimodal age distribution
- age-related tremor („senile tremor“)
 - different clinical signs, course, and prognosis compared to patients with early-onset ET
 - higher risk of dementia
 - higher risk of gait and balance disorders
 - more frequent coincidence with PD

Rajput 1984, Louis 2007, Louis 2010, Deuschl 2015

Diagnosis of Essential Tremor (ET)

ET with associated signs = ET plus syndromes

- dystonia
- bradykinesia + rigidity
- disorders of gait and stability
- cognitive dysfunction

Various etiological entities with ET syndrome as initial manifestation

If unclear, the patient should be seen by a movement disorders specialist

Essential tremor „plus“

Tremor with the characteristics of ET

+ additional neurological signs of uncertain significance

- impaired tandem gait
- questionable dystonic posturing
- memory impairment
- or other mild neurologic signs that do not suffice to make an additional syndrome classification or diagnosis

Bhatia et al. 2018

If unclear, the patient should be seen by a movement disorders specialist

Other tremor syndromes – differential diagnosis of ET

- tremor associated with dystonia
- action tremor combined w. rest tremor and/or parkinsonism
- enhanced physiologic tremor
- intention tremor (cerebellar, rubral tremor)
- functional (psychogenic) tremor
- tremor in Wilson's disease

Differential diagnosis of ET

Isolated head tremor (+ cervical dystonia)

- dystonic tremor: at the body part affected by dystonia
 - most often head tremor in cervical dystonia

– increased probability of segmental spread of dystonia
 – often positive family history → genetic component suspected



- tremor associated with dystonia: at a different body part

Cannot be classified essential tremor according the new criteria!

Differential diagnosis of ET

ET combined with resting tremor or parkinsonism

- additional features of PS in 6/20 (30%)
- ET + resting tremor in other 6, with no identifiable pathology

Essential tremor course and disability A clinicopathologic study of 20 cases

Alexander Rajput, MD, FRCPC; Christopher A. Robinson, MD, FRCPC; and Ali H. Rajput, MBBS, FRCPC

Rajput 2004

One of the situations when DaTSCAN SPECT can be helpful

Differential diagnosis of ET

Enhanced physiological tremor

Definition: symptomatic upper extremity action tremor that is potentially reversible if the cause of the tremor is eliminated

Phenomenology:

- bilateral upper limb action tremor due to enhancement of the normal mechanical reflex and 8- to 12-Hz central neurogenic oscillations

Etiology:

- a variety of reversible conditions, such as anxiety, fatigue, hyperthyroidism, and drugs (lithium, tricyclic antidepressants, valproate, sympathomimetics, etc.)

Most common differential diagnosis: ET, but duration of enhanced physiological tremor is usually far less than 3 years.

Cerebellar tremor

- intention tremor
 - usually with postural component
 - slow (below 4 Hz)
 - asymmetric
- titubation
- ataxia and hypermetria contribute to disability



Differential diagnosis of ET **Wilson's disease**

- tremor among most prevalent motor manifestations
(other: dysarthria, dystonia, parkinsonism)



to be excluded in any movement disorder \leq 45 yrs !!!

Investigation results

- **brain MRI: non-specific intensity changes in the brainstem and basal ganglia**
- **blood: low ceruloplasmin, increased free copper**
- **urines: high copper excretion**
- **in addition: Kayser-Fleischer ring, ATP7B mutation (homozygous for His1069Gln)**



Functional tremor

INCONSISTENCY

- variability of amplitude, frequency, distribution
- **distractibility, suggestibility, suppressibility**
- frequency entrainment
- disability is disproportionate to objective findings



Functional tremor

INCONGRUENCE

- mixed, bizarre signs
- do not present or progress according to known organic phenotypic patterns
- non-anatomical distribution
- **antagonistic muscle coactivation**
- **inadequate pain or sensory involvement**



Treatments for ET

MDS COMMISSIONED REVIEW

Check for
update

MDS Evidence-Based Review of Treatments for Essential Tremor

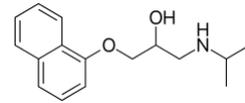
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Eng-King Tan, MD,⁶ Giovanni Abbruzzese, MD,⁷ Mark Hallett, MD,⁸ Dietrich Haubenberger, MHSc, MD,⁹
Rodger Elble, MD PhD,¹⁰ and Günther Deuschl, MD, PhD,¹¹
on behalf of MDS Task Force on Tremor and the MDS Evidence Based Medicine Committee

Treatments for ET

<i>drug</i>	<i>efficacy</i>	<i>safety</i>
propranolol	efficacious	acceptable risk without specialized monitoring
primidone	efficacious	acceptable risk without specialized monitoring
topiramate (> 200 mg/day)	efficacious	acceptable risk with specialized monitoring
VIM DBS	likely efficacious	acceptable risk with specialized monitoring

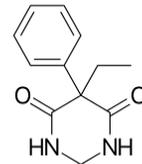
Ferreira et al. 2019

Propranolol



- effective in about 60 % patients
- tremor reduced by approx. 50 %
- start with 10-20 mg per day, can increase up to 60-90 mg daily
- side effects: postural hypotension, bradycardia, possible breathing difficulties in those with a history of asthma; erectile impotence

Primidone



- benefit in 30 – 50 % patients
- reduces tremor by 50 – 70 % at doses 150-300 mg per day
- moderate to high frequency of adverse events: sedation, nausea, vomiting, vertigo, confusion, especially at doses higher than 500 mg per day
- often as acute toxic reaction to the first dose
- problematic, particularly in older patients
- occasional difficulties with withdrawal after long-term use
- start carefully on very low dose (25 mg or less), titrate slowly

Alcohol in ET ?

- **temporary amelioration of tremor following ethanol ingestion reported in 45–75% of ET patients**

(Growdon 1975, Lou and Jankovic 1991, Bain 1994)

- **ataxic gait in advanced ET improves with ethanol** *(Klebe 2005)*



Avoid Alcohol For Hand Tremors

Studies to determine whether essential tremor is a risk factor for alcoholism have been inconsistent

JUNE, 1949

BRAIN

VOL. 72, PART 2.

OBSERVATIONS ON ESSENTIAL (HEREDOFAMILIAL) TREMOR

BY

MACDONALD CRITCHLEY

Journal of Neurology, Neurosurgery, and Psychiatry 1984;47:466-470**Essential tremor in Rochester, Minnesota: a 45-year study**

AH RAJPUT,* KENNETH P OFFORD,† C MARY BEARD,‡ LT KURLAND†

From the Department of Clinical Neurological Sciences, University of Saskatchewan, College of Medicine, Saskatoon, Saskatchewan, Canada, and the Department of Medical Statistics and Epidemiology, Mayo Clinic, Rochester, Minnesota, USA†*Movement Disorders
Vol. 25, No. 14, 2010, pp. 2274-2284
© 2010 Movement Disorder Society**CME**

Review

Alcohol in Essential Tremor and Other Movement DisordersGiovanni Mostile, MD, PhD^{1,2} and Joseph Jankovic, MD^{1*}¹*Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas, USA*²*Department of Neurosciences, University of Catania, Catania, Italy*

„Some patients find that a heavy dose of spirits will temporarily check the tremor and this factor has appeared only too often to have served as an excuse for habits of intemperance“

- **266 ET cases diagnosed during 45 years**
- **„excessive use“ of alcohol in 16 % and alcoholism diagnosed in 6 %**

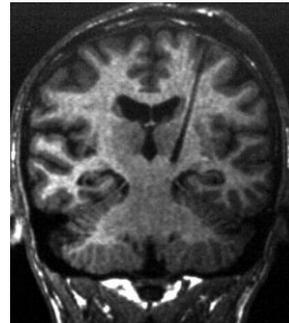
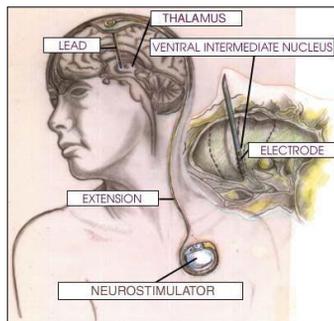
„...case control studies on alcohol use in patients with ET did not reveal any significant risk of abuse“

Pharmacotherapy of tremors other than ET

- **therapy of underlying cause (if known and treatable)**
 - **drug-induced tremors, intoxications**
 - **endocrine and metabolic disorders**
 - **Wilson's disease**
 - ...
- **symptomatic pharmacotherapy**
 - **Parkinson's disease (levodopa)**
 - **dystonic tremor (botulinum toxin)**
 - **cerebellar tremor (if causal disease treatable)**
 - ...

Functional neurosurgery: VIM

- nucleus ventralis intermedialis (VIM) thalami: target for modulation of tremor of any origin
 - thalamotomy
 - deep brain stimulation (DBS)



DBS VIM in essential tremor



DBS VIM „off“



DBS VIM „on“

Must be performed in an experienced movement disorders center

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