Essential Tremor: What’s New?

Update on a deceptively simple movement disorder

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Overview

• Evolving concept of ET
  – *It's getting complicated* …

• Research on new treatments of ET
  – long-chain alcohols – the NIH studies
  – Focused ultrasound
How common is tremor?

- Population-based study in Bruneck, South Tyrol
  - Entire population aged 50-85: n=708
  - Tremor total: 14.5%
  - Enhanced physiological tremor: 9.5%
  - Essential Tremor: 3.1%
  - Parkinsonian Tremor: 2.8%
  - Cerebellar Tremor: <0.2%

Wenning, Lancet Neurol, 2005

How common is ET?

- Pooled analysis from 28 population-based studies:
  - World-wide population-prevalence estimated at 0.9% across all ages
  - Risk-factor age: by age 70, median prevalence: 6.3% (range 2.3 – 14.3%)
  - Majority of studies did not show gender-effect
  - No systematic data on effects of ethnicity
  - Limitations:
    - Sensitivity/specificity of screening procedures
    - Varying definition of ET

Louis and Ferreira, Mov Disord, 2010
Defining ET

- Currently 3 definition criteria in use

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<thead>
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<tbody>
<tr>
<td>Topography</td>
<td>Bilateral hands/arms</td>
<td>Bilateral hands/arms</td>
<td>Bilateral hands/arms</td>
</tr>
<tr>
<td>Activation</td>
<td>Posture +/- kinetic</td>
<td>Posture +/- kinetic</td>
<td>Posture + kinetic</td>
</tr>
<tr>
<td>Isolated Head tremor?</td>
<td>Allowed</td>
<td>Not allowed</td>
<td>Not allowed</td>
</tr>
<tr>
<td>Intensity requirement</td>
<td>&quot;visible and persistent&quot;</td>
<td>&quot;visible and persistent&quot;</td>
<td>&gt;1cm amplitude</td>
</tr>
<tr>
<td>Duration</td>
<td>n/a</td>
<td>&gt;5 years</td>
<td>n/a</td>
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- Common exclusion criteria
  - "other abnormal neurological signs", especially enhanced physiological tremor, psychogenicity, dystonia, isolated/task-specific tremors

ET: challenging diagnosis

- Common misdiagnosis?

"Half of the patients (47%) had associated dystonia, including cervical dystonia, writer’s cramp, spasmodic dysphonia, and cranial dystonia, and 20% of the patients had associated parkinsonism."

- "True" ET vs. "normal" tremor?
Own experience

• Screening protocol for the Octanoic Acid trial
  – Prescreened via phone 216
    • Didn’t meet ET criteria 47 (22%)
      Tremor not bilaterally
      Tremor not affecting hands/arms
      Coexisting neurological signs such as dystonia, parkinsonism
  – Screened in-person 29
    • Didn’t meet ET criteria 7 (29%)
      Tremor not visible/persistent
      Other tremor-cause: psychogenic, dystonic, parkinsonian tremor

When tremor is normal:

Physiological Tremor

• No object in space is perfectly still
  – Laws of physics!
  – Example: oscillation of a bridge
  – Limbs are subject to oscillations as well
• Many rhythmical process in the body:
  – Heartbeat
  – Muscle activation
  – Nerve cell firing
• When normal limb oscillation becomes visible: enhanced physiological tremor
  – Medication side effect: Asthma-Meds, Antidepressants, Anticonvulsants, ...
  – Under certain disease conditions: impaired kidney/liver function, thyroid dysfunction
  – Physical reasons: shivering
  – Withdrawal symptoms

➢ By far the most common cause for tremor in the elderly!
  Looks just like ET!
Tremor with a Twist: Dystonia

• Dystonia: involuntary movement disorder with sustained muscle contraction which leads to a turn or twist e.g. of a limb or the neck.
• Can be accompanied by tremor of the affected limb or of a different body part
• Examples:
  – Cervical Dystonia
  – Writers Cramp
  – Spasmodic dysphonia

Dystonia in „true“ ET?

• 97 families with ET
• 463 subjects examined
• Dystonia present in 27 out of 97 ET families
  – Subtype of ET involving dystonia?
  – Dystonia, ET separate phenotypes of same genetic background?
Don't underestimate the mind: 
*Functional Tremor*

- Previously called: Psychogenic tremor
- **Involuntary** movement disorder, mimicking voluntary tremor!
- Actual disorder, not an exclusion diagnosis
- Comparabale to other psychosomatic conditions:
  - Body-symptoms due by psychological/psychiatric cause (e.g. like upset stomach during times of psychological stress)
  - All physical exams (MRI, etc.) typically normal
- Can look like ET, but shows more often:
  - Sudden onset, e.g. after a physical or psychological trauma event
  - Atypical picture: e.g. only one-sided tremor
  - Association with other psychiatric disease: depression, PTSD, etc.
- **Acceptance of diagnosis is low**
- **However:** if recognized early and the underlying cause is treated, tremor can resolve!

**Summary I**

ET, a simple movement disorder?

- Rates of both false diagnoses as well as missed diagnoses are high
- Disagreement / lack of understanding in the field of doctors not uncommon
- Resulting in so far disappointing research on cause of ET (e.g. genetics, etc.)

- ET as syndrome / spectrum rather than single disease?
- New classification on tremor announced:
  - MDS Task Force on Tremor
Treatment of ET
- a dilemma

- No change in treatment recommendation since 2005 (AAN Practice Parameters 2011; Deuschl et al, 2011)
- Documented drug-treatment effect in studies moderate at best
- Treatment often limited due to acute or long term tolerability problems
- Retrospective treatment experience in 200 ET patients (P Bain, MDS 2010):

<table>
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<tr>
<th>Substance</th>
<th>n</th>
<th>% Responder</th>
<th>% AEs</th>
<th>% Discontinued</th>
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<tbody>
<tr>
<td>Propranolol</td>
<td>99</td>
<td>43</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Primidone</td>
<td>70</td>
<td>33</td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td>Topiramate</td>
<td>40</td>
<td>35</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>20</td>
<td>30</td>
<td>35</td>
<td>70</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>19</td>
<td>21</td>
<td>53</td>
<td>74</td>
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1-octanol: effect in the animal model

- 1-octanol *in vitro* blocks the low threshold Ca\(^{2+}\) channel (LTCC) in the IO and thalamus (Jokovic et al, 2010; Llinas et al, 1986)
- 350 mg/kg 1-octanol significantly reduced harmaline-induced tremor in mice (Martin et al, 2005)
- Maximum tolerated dose: 1,000 mg/kg (Nahab et al, 2012)
- In the animal model of tremor, octanol showed best safety/efficacy profiles compared to other long-chain alcohols (Sinton et al, 1989; Martin et al, 2005)
Pilot trial of 1-octanol in essential tremor

K.O. Bushara, MD; S.B. Goldstein, MD; G.J. Grimes, Jr, PharmD; A.H. Barstein, PharmD; and M. Hallett, MD

Abstract—1-Octanol (a N.C. alcohol currently used as a food-flavoring agent) is known to inhibit tremor in essential tremor (ET). Animal models in a much lower dose than ethyl alcohol. The authors conducted a randomized, placebo-controlled, pilot trial of a single oral dose of 1 mg/kg of 1-octanol in 12 patients with ET. No significant side-effects or signs of intoxication were observed. 1-Octanol significantly decreased tremor amplitudes for up to 90 minutes. The results suggest 1-octanol as a well-tolerated and safe potential treatment for ET. Further trials are warranted.

NEUROLOGY 2014;83:124-128

Open-label dose-escalation study of oral 1-octanol in patients with essential tremor

H.A. Skull, MD; K.O. Bushara, MD; E. Mars, MD; M. Reisch, and M. Hallett, MD

Abstract—Twenty-one single oral dose of 1-octanol were given to patients with essential tremor (ET) in an open-label dose-escalation study. The drug was well tolerated up to 94 mg/kg. The main side effect was an unusual taste. No overt intoxication was seen. There was evidence for efficacy, with a significant reduction in tremor amplitude as measured by seismometry and handwriting that was sustained at 2 hours. Higher doses may produce more sustained benefit.


Efficacy, Safety

![Graph showing tremor reduction with 1-octanol](image)

**CNS and PNS disorders**

- Fatigue: 5 (20%)
- Dizziness: 2 (10%)
- Nausea: 3 (15%)
- Drowsiness: 1 (5%)
- Vertigo: 1 (5%)

**Gastrointestinal**

- Abdominal pain: 1 (5%)
- Diarrhea: 5 (25%)
- Nausea: 1 (5%)
- Vomiting: 6 (30%)
- Constipation: 1 (5%)

**Cardiovascular**

- Hypertension: 4 (19%)
- Tachycardia: 2 (10%)

**Psychiatric disorders**

- Dry mouth: 4 (19%)
- Constipation: 3 (15%)
- Fatigue: 1 (5%)

**Visual disorders**

- Blurred vision: 2 (10%)
- Drowsiness: 3 (15%)
- Dry eyes: 1 (5%)
1-octanol pharmacokinetics

- Only minimal 1-octanol plasma-response
- Significant rise in octanoic acid levels
- Dose-dependent octanoic acid plasma response

Background: Octanoic Acid

- OA is approved as food additive by FDA (GRAS)
- Nutritional studies: safe in humans up to 700 mg/kg
- Acute oral LD50 (rat): 10.08 g/kg
- Naturally present in coconut and lemon oil
- Permeates into the brain-space well in the rat: 94% brain uptake after injection into artery
- Similar effect in the animal model of ET than octanol

Jenner et al, 1964; Sills et al, 1986; Carnelli et al, 1994; Ashitani et al, 2009; Oldendorf, 1973
09-N-0084
Safety and efficacy trial – Octanoic Acid in ET

• Pilot trial assessing safety and efficacy of Octanoic Acid (OA) in ET (NCT00848172)
  - Double-blind placebo controlled cross-over trial
  - n=19 ethanol responsive ET subjects
  - Single-dose administration, on two consecutive days during inpatient stay at NIH-CC
  - Dose: 4 mg/kg, orally administered (capsule)

• Study outcomes
  - Efficacy: Accelerometry, Spirography
    - Primary Outcome: Dominant hand postural tremor power of the central tremor component (accelerometry), 80min post OA compared to placebo
  - Safety: Intoxication scale, Lab-Panel, EKG, AE screen, Vital signs
  - Pharmacokinetic sampling

• Study failed to meet its primary outcome
  - No difference in dominant hand tremor 80min post administration

• Secondary outcomes:
  - significant differences at 300 min
  - additionally at 180 min when both hands analyzed together
  - statistical trend starting at 150 min

Haubenberger et al, Neurology, 2013
Secondary outcomes

• Within-subject analysis (OA minus Placebo effect)
  – Significant effect over time for dominant hand \((p<0.001)\), and both hands \((p<0.0001, \text{Friedman test})\)

• No effect seen in spiral analysis

Safety

• 2 serious adverse events – both unrelated to OA

• Non-serious AEs were mild and transient
  – Total \(n=26\)
  – No taste changes
  – Most common: fatigue \((n=5)\), headache \((n=3)\)

• No change in laboratory parameters, EKG, vital signs

• No signs of intoxication
Results: Pharmacokinetics

• Sampling available from 18 subjects (5f, mean age 61.4±9.9)
• Mean dose administered: 352.8 ± 69.9 mg

• Maximum concentrations reached at ~70 min ($t_{\text{max}} = 72.8 \pm 34.3$ min)
  • Volume of distribution ($V_d/F$) = 389 L
  • Average clearance (CL/F) = 186.8 L/hr
  • Average elimination half life $t_{1/2} = 83.5$ min
  • Terminal elimination rate constant $\lambda_z = 0.0098$ min$^{-1}$

Conclusion: Octanoic Acid Trials

• Up to 128 mg/kg oral OA are safe in subjects with ET
• Primary efficacy outcome (low dose study) was not met
• Placebo-controlled data suggests efficacy at later time-points

• Effect longer lasting than anticipated
Octanoic acid

Next steps

• Further escalation using efficient clinical trial designs
• Placebo-controlled, long-term administration study
• Optimization of formulation (liquid?)
• Optimization of outcome measures
  – Goal: improvement of tremor in daily life tasks
  – Patient reported outcomes (health-related QoL, etc.)

• Phase 1, uncontrolled, open-label study
• 15 Patienten mit severe, treatment resistant ET
• Unilateral ultrasound-thermo-ablation of ViM nucleus of the thalamus
• Performed in MRI scanner
• Outcome: tremor rating scale, quality of life scale, disability score
• Safety: strength, sensibility, gait, MRI
• F/U: up to 1 year
• "sonications" for 10-20 sec each
• Tremor assessment after each sonication
• Rising temperatur
  – Reversible effect at 40-45 degC - calibration
  – Permanent effect at 55-63 degC

Results
Outlook

- Cause of ET still largely based on hypotheses
- Break-through in ET genetics still awaited
- Change in concept of ET from single disorder to syndrome likely
- Experimental ET therapies: translation into routine treatment?
  - Long-chain alcohols
  - Non-invasive brain stimulation: Elias WJ et al, NEJM 2013
Thank you!

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