Movement Disorders translational research to bridge into clinical practice

Essential tremor
45 min

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Stockholm September 2012
Clinical Classification

1998 MDS Classification

• Bilateral action tremor of the hands and forearms (but not rest tremor)
• Absence of other neurologic signs with the exception of the cogwheel phenomenon
• May have isolated head tremor with no signs of dystonia

3 years: probable ET, >5 years: definite ET
The prevalence of tremor in different studies worldwide: are these all the same tremors?

Louis and Ferreira 2010
The border to dystonic tremor
(Ferraz et al. 1994)

- 22.7% of idiopathic dystonias have a significant tremor
- 21.5% of symptomatic dystonia have a significant tremor

Similar percentage for focal, segmental and generalized dystonia
Essential or dystonic tremor
The diagnostic significance of the ‘geste antagoniste’ for detecting essential versus dystonic head tremor
Quantification of sensory trick: impact on tremor amplitude and frequency in 60 patients with head tremor (Masuhr et al. 2000)

<table>
<thead>
<tr>
<th></th>
<th>Definition</th>
<th>No of patients</th>
<th>Clinical positive geste</th>
<th>Reduction of tremor (peak power)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremulous Cervical dystonia</td>
<td>Head tremor and torticollis</td>
<td>34 patients</td>
<td>+</td>
<td>83%</td>
</tr>
<tr>
<td>Dystonic head tremor</td>
<td>Head tremor without torticollis</td>
<td>14 patients</td>
<td>+</td>
<td>90%</td>
</tr>
<tr>
<td>Essential head tremor</td>
<td>Head tremor without torticollis</td>
<td>12 patients</td>
<td>-</td>
<td>6%</td>
</tr>
</tbody>
</table>
## Differential diagnosis between dystonic an essential tremor

<table>
<thead>
<tr>
<th></th>
<th><strong>Dystonic tremor</strong></th>
<th><strong>Essential tremor</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Gradual onset (over years)</td>
<td>Gradual onset (over decades)</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>rare</td>
<td>frequent</td>
</tr>
<tr>
<td><strong>Focal tremor</strong></td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Gestes antagonistiques</strong></td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Alcohol-sensitivity</strong></td>
<td>unknown</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Distractability</strong></td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td><strong>Variability</strong></td>
<td>Task-consistent</td>
<td>low</td>
</tr>
<tr>
<td><strong>Co-contraction</strong></td>
<td>May occur</td>
<td>rare</td>
</tr>
<tr>
<td><strong>Finger tremor</strong></td>
<td>frequent</td>
<td>frequent</td>
</tr>
</tbody>
</table>
Clinical evidence for a subdivision?

Do we have sufficient evidence for separating ET-cases beyond the general definition?
Essential Head Tremor Is Associated with Cerebellar Vermis Atrophy: A Volumetric and Voxel-Based Morphometry MR Imaging Study

BACKGROUND AND PURPOSE: Our aim was to investigate the presence of brain gray matter (GM) abnormalities in patients with different forms of essential tremor (ET).

MATERIALS AND METHODS: We used optimized voxel-based morphometry (VBM) and manually traced single region-of-interest analysis in 50 patients with familial ET and in 32 healthy subjects. Thirty patients with ET had tremor of the arms (a-ET), whereas the remaining 20 patients had both arm and head tremor (h-ET).

RESULTS: VBM showed marked atrophy of the cerebellar vermis in the patients with h-ET with respect to healthy subjects ($P_{\text{corrected}} < .001$). Patients with a-ET showed a trend toward a vermal GM volume loss that did not reach a significant difference with respect to healthy controls ($P_{\text{corrected}} < .01$). The region-of-interest analysis showed a reduction of the cerebellar volume (CV) in the h-ET group (98.2 ± 13.6 mm³) compared with healthy controls (110.5 ± 16.6 mm³, $P < .012$) as well as in the entire vermal area (790.3 ± 244.5 mm², 895.6 ± 170.6 mm², $P < .04$ in h-ET and control groups, respectively).

Vermis lobule IV
($x = 3; y = -51; z = -14$)
Voice tremor:
Possible hints at the differential diagnosis

ET-voice tremor
Vocal speech

ET voice tremor an intervention
before after

Dystonic voice tremor

Vocal speech
Clinical Classification

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2013 MDS Classification (work in progress)
- Axis 1 (Syndromic classification): bi-brachial symmetrical postural and kinetic tremor syndrome of both arms with or without head tremor, with or without additional symptoms
- Axis 2 (Etiologic classification): Clinically isolated tremor with or without additional symptoms to be defined
Long-term course of ET: Disease progression, another tool?

- Mean annual increase of tremor severity: 12% worsening (Putzke et al. 2006).
  - Factors with severity at initial visit: older age, longer disease duration, voice tremor.
  - Factors with progression after initial visit: asymmetrical tremor, longer follow-up

- Mean annual increase in tremor severity: 3.1 – 5.3%. Median annual increase: 1.8%-2.0% (Louis et al 2011)
Does pathology help to define ET?

19 cases since the 1930-ies - inconsistent pathology

Rajput et al 2004: 20 cases - inconsistent pathology

Controlled studies (57 cases):
Louis et al. (5 papers reporting a total of 33 patients):
2 types of pathology:
    ET with Lewy bodies
    ET without Lewy bodies, Purkinje cell ↓, Torpedos ↑

Shill et al. 2008 (1 paper on 24 patients):
    Significant cerebellar pathology and atrophy of the locus coeruleus but no Lewy bodies

Rajput et al. 2012 (12 ET, 6 controls, 41 PD)
    Purkinje-cell loss is age-dependent, not ET-specific
Is this the pathology?

Purkinje cells

Torpedoes

Louis et al. Brain 2007
Mean number of Purkinje cells

controls  ET with LB  ET without LB  controls  ET with LB  ET without LB

25 cases without Lewy bodies  8 cases with Lewy bodies

* ns

* ns

Louis et al. Brain 2007
Purkinje cell axonal anatomy: quantifying morphometric changes in essential tremor versus control brains

Rachel Babij,1 Michelle Lee,1 Etty Cortés,2 Jean-Paul G. Vonsattel,2,3 Phyllis L. Faust3 and Elan D. Louis1,2,4,5

Torpedos on axons with recurrent collaterals
## Quantitative measures

<table>
<thead>
<tr>
<th></th>
<th>ET-Cases</th>
<th>Controls</th>
<th>significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purkinye cell count</td>
<td>6.6 ± 1.7</td>
<td>9.9 ± 3.1</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Torpedo count (Bielschowsky)</td>
<td>25.0 ± 27.7</td>
<td>9.2 ± 9.5</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>87.8 ± 71</td>
<td>77.4 ± 12.0</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Essential tremor: 49 cases
Controls: 39 cases

Babij et al. 2013
Cerebellar Purkinje cell loss is not pathognomonic of essential tremor

A.H. Rajput*, C.A. Robinson, M.L. Rajput, A. Rajput

Saskatchewan Health Region, University of Saskatchewan, Room 1663, Royal University Hospital, Saskatoon, Saskatchewan S7N 0W8, Canada

Parkinsonism and Related Disorders 17 (2011) 16–21
Pathology continues to be inconsistent

<table>
<thead>
<tr>
<th></th>
<th>ET comes with Lewy pathology</th>
<th>ET comes with obvious cerebellar pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louis et al. 2009</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Shill et al. 2008</td>
<td>No</td>
<td>Some cases</td>
</tr>
<tr>
<td>Rajput et al. 2011</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
Does genetics help to redefine ET?
Candidate genes

- **ETM1**: (FET1) (4 of 6 cohorts positive)
  DRD3: Dopamine receptor D3 may involved in regulation of locomotion. DRD3 is expressed in Purkinje cells

- **ETM2**: (5 of 7 cohorts)
  HS1-BP3 gene: HS1-BP3 protein binds to proteins that are expressed in neurons and Purkinje cells and regulates Ca2+ calmodulin-dependent protein kinase activation of tyrosine and tryptophan hydroxylase

- **GABA A receptor α1 & GABA transporter subtype 1**
  knock out mice (2 negative studies)

Replication studies failed for most of the loci except for ETM 2.
Genome-wide association studies: The LINGO1-gene (Steffanson, Nat Med 2009)

Stefansson et al. 2009: 450 cases, 300 follow-up, 15,000 controls. Significant association on chromosome 15q24.3 (SNP: rs9652490(G))
Lingo1 metaanalysis

Kuhlenbäumer et al (in preparation)

Diagnostic OR (95% CI)

- Stefansson, 2009 Ref 2: 1.73 (1.16 - 2.56)
- Stefansson. 2009 Ref 2: 1.39 (0.90 - 2.16)
- Stefansson. 2009 Ref 2: 1.32 (0.96 - 1.81)
- Stefansson. 2009 Ref 2: 1.29 (0.74 - 2.26)
- Tan, 2009 Ref 43: 1.28 (0.98 - 1.65)
- Thier, 2010 Ref 40: 1.65 (1.24 - 2.19)
- Thier. 2010 Ref 40: 1.71 (1.02 - 2.86)
- Clark, 2010 Ref 42: 1.33 (0.99 - 1.79)
- Zuo, 2010 Ref 44: 0.98 (0.68 - 1.42)
- Vilarino-Guell, 2010 Ref 39: 0.80 (0.63 - 1.02)
- Vilarino-Guell, 2010 Ref 41: 0.94 (0.80 - 1.10)
- Wu, 2011 Ref 45: 0.96 (0.65 - 1.42)
- Bourassa, 2011 Ref 38: 1.02 (0.78 - 1.32)
- Lorenzo-Betancor, 2011 Ref: 0.87 (0.66 - 1.16)
- Radovica, 2012 Ref 46: 1.02 (0.66 - 1.55)

Pooled Diagnostic Odds Ratio = 1.09 (1.02 to 1.17)
Excitatory amino-acid transporter 2 (EAAT2) = solute carrier family 1 member 2 (SLC1A2)

Thier et al. 2012

990 subjects and 1,537 control subjects from Kiel, Innsbruck, Tübingen, Odense

1. Step: Assoziation von rs3794087, p=6.95x10^{-5}, OR=1.46).
2. Step: Association of rs3794087, p=1.25x10^{-3}, OR=1.38).

SLC1A2 / EAAT2 important transmembraneous glutamate transporter
A family with a FUS p.Gln290* Mutation as the cause of ET

For 270 additional cases only 2 missense mutations

FUS mutations found in ALS are different and do have more severe functional consequences.

Confirmation: 1 other family, several attempts failed
Does epidemiology help to define essential tremor?
Epidemiological data are inconsistent:
Two large epidemiological studies in New York and Spain

- Prevalent dementia increased in ET (OR= 1.84, 95% CI = 1.13-2.98, p = 0.01). (Thawani et al. 2009)
- Prevalent dementia not increased in the whole population but in those ET with onset >65 y (Bermejo-Pareja et al. 2007)
- Incident dementia increased in ET with onset > 65 y (Benito-Leon et al. 2011)
- Higher mortality in ET (Louis et al., 2007)
Longevity in ET

Table 2. Age of parents at death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parents of PD patients with tremor</th>
<th>Parents of PD patients without tremor</th>
<th>Parents of ET patients without tremor</th>
<th>Parents of ET-PD patients with tremor</th>
<th>Parents of ET-PD patients without tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>47</td>
<td>572</td>
<td>145</td>
<td>58</td>
<td>146</td>
</tr>
<tr>
<td>Median age at death of mothers (yr)</td>
<td>85</td>
<td>82</td>
<td>80*</td>
<td>83</td>
<td>80</td>
</tr>
<tr>
<td>Median age at death of fathers (yr)</td>
<td>84†</td>
<td>73†</td>
<td>70*</td>
<td>82†</td>
<td>62†</td>
</tr>
</tbody>
</table>

PD  Parkinson’s disease.
ET  Essential tremor.
ET-PD  Combined essential tremor and Parkinson’s disease.
*  $p < 0.05$.
†  $p < 0.005$. 

Jankovic 1995
The influence of age
(mean values of 10 studies)

Mean prevalence

Data from Louis and Fereira MDJ 2010
When is full penetrance reached in hereditary ET?

A study of hereditary essential tremor


*Brain* (1994), **117**, 805–824
Preliminary conclusions

- Clinical analysis suggests subtyping
- Pathology inconsistent
- Biochemistry inconsistent
- ET prevalence is increasing with age
- Hereditary ET (the core group) is fully penetrant above the age of 65
- May or may not be associated with prevalent and incident dementia
- May or may not be associated with shorter life expectancy
Tremor in the elderly: Results from a Danish cohort of aging twins

LSADT 2001 participants of 2001 wave
N=2,448

2,414 individuals
1,379 from broken pairs
1,035 from intact pairs

- Self-reported Parkinson's disease or users or antiparkinsonia (N=34)

2,327 individuals (2,035 with a spiral score)
1,311 from broken pairs (1,112 with a spiral score)
1,016 from intact pairs (923 with a spiral score)

- Proxy-interviewed (N=87)

269 neurologically assessed
22 from broken pairs (22 with a spiral score)
247 from intact pairs (229 with a spiral score)

2,058 not neurologically assessed
1,289 from broken pairs (1,090 with a spiral score)
769 from intact pairs (694 with a spiral score)
Spiral-grading of 2403 persons with an age >70 years

Tremor grading

0 1 2 3 4 5 6 7
0 100 200 300 400 500 600 700 800
Tremor Score is increasing with age
The spiral score is logarithmically related to the Fahn tremor scale.
The hazard ratio for mortality is increasing with higher spiral scores.

<table>
<thead>
<tr>
<th>Spiral score</th>
<th>HR 1</th>
<th>n=783</th>
<th>HR 1.23</th>
<th>n=692</th>
<th>HR 1.46</th>
<th>n=368</th>
<th>HR 1.84</th>
<th>n=194</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>reference</td>
<td>p=0.01</td>
<td>p&lt;0.01</td>
<td>p&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Kaplan-Meier curves
(Males and females)

- Black line: Spiral score 0-2
- Green line: Spiral score 3
- Blue line: Spiral score 4
- Red line: Spiral score 5-7
Classical aging parameters are worsening with higher spiral scores

<table>
<thead>
<tr>
<th>Spiral score</th>
<th>N^a</th>
<th>Grip strength (kg) (95%CI)</th>
<th>Cognitive composite (95%CI)</th>
<th>ADL Strength score (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>783</td>
<td>Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>692</td>
<td>-0.75 (-1.35;-0.15)</td>
<td>-1.12 (-1.46;-0.77)</td>
<td>-0.10 (-0.16;-0.04)</td>
</tr>
<tr>
<td>4</td>
<td>368</td>
<td>-0.90 (-1.66;-0.14)</td>
<td>-1.58 (-2.00;-1.15)</td>
<td>-0.13 (-0.20;-0.05)</td>
</tr>
<tr>
<td>5-7</td>
<td>194</td>
<td>-2.99 (-4.13;-1.85)</td>
<td>-2.57 (-3.11;-2.03)</td>
<td>-0.36 (-0.47;-0.24)</td>
</tr>
</tbody>
</table>
The spiral score is an independent predictor for mortality tremor cases (spiral s. > 3) vs. non-tremor cases (spiral s. ≤ 3)

<table>
<thead>
<tr>
<th>Adjusted for</th>
<th>Age, sex</th>
<th>Age, sex, and medication</th>
<th>Age, sex, grip strength, ADL strength score, and cognitive and functioning</th>
<th>Age, sex, grip strength, ADL strength score, and cognitive and functioning, and all medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2,037</td>
<td>2,037</td>
<td>1,952</td>
<td>1,952</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.45 (1.27;1.66)</td>
<td>1.43 (1.26;1.63)</td>
<td>1.21 (1.05;1.40)</td>
<td>1.21 (1.05;1.40)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
What about essential tremor patients?
The hazard ratio is lower for essential tremor.
ET-patients have a significantly longer life expectancy than all subjects of the aging population

<table>
<thead>
<tr>
<th>Tremor groups vs other participants</th>
<th>Reference group (n)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite ET (n=34)</td>
<td>2,035</td>
<td>0.52 (0.31-0.90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Probable ET (n=67)</td>
<td></td>
<td>0.83 (0.61-1.13)</td>
<td>0.25</td>
</tr>
<tr>
<td>Other tremors (n=17)</td>
<td></td>
<td>1.06 (0.58-1.93)</td>
<td>0.86</td>
</tr>
<tr>
<td>Intact pairs only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitely ET (n=29)</td>
<td>923</td>
<td>0.45 (0.23-0.858)</td>
<td>0.02</td>
</tr>
<tr>
<td>Probable ET (n=58)</td>
<td></td>
<td>0.77 (0.53-1.13)</td>
<td>0.18</td>
</tr>
<tr>
<td>Other tremors (n=13)</td>
<td></td>
<td>1.37 (0.64-2.97)</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Aging parameters are better for ET patients

<table>
<thead>
<tr>
<th>Tremor group</th>
<th>N*</th>
<th>N* (ref. group)</th>
<th>Grip strength (95% CI)</th>
<th>Cognitive composite (95% CI)</th>
<th>ADL strength score (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite ET</td>
<td>31</td>
<td>2,298</td>
<td>0.10 (-2.16;2.36)</td>
<td>0.73 (-0.25;1.70)</td>
<td>0.14 (-0.02;0.28)</td>
</tr>
<tr>
<td>Probable and possible ET</td>
<td>61</td>
<td></td>
<td>-0.23 (-2.09;1.63)</td>
<td>-0.23 (-0.11;0.66)</td>
<td>0.09 (-0.05;0.22)</td>
</tr>
<tr>
<td>Other tremors</td>
<td>22</td>
<td></td>
<td>-3.90 (-6.17;-1.62)</td>
<td>-0.87 (-2.50;0.75)</td>
<td>-0.60 (-0.94;-0.25)</td>
</tr>
</tbody>
</table>

* Definite ET group is compared to the reference group.
Tremor and aging: A hypothesis on tremor in the elderly
Conclusion

Essential tremor
- Full penetrance is reached in families with ET at age 65
- Evidence for longevity in ET

Senile (age-related) tremor
- Epidemiologic evidence for an age-related tremor
- If tremor starts after the 6th decade (65?):
  - More frequent dementia
  - Shorter life span after tremor onset

**ET is not a unique disease**
- Senile tremor is probably the largest subgroup of „ET“
- Classical hereditary ET the 2nd largest
- Sporadic ET in children and adults < 65 years the 3rd largest
Coworkers in Kiel:
Delia Lorenz
M. Muthuraman
Christine Daniels
Jan Raethjen
Frank Papengut
Kirsten Zeuner
Helge Hellriegel
Thilo v. Eimeren
Karina Knudsen
Stefan Klebe
Jens Volkmann
Caroline Poremba
Henning Stolze
Henrik Wilms
Meike Steinbach

Coworkers elsewhere:
Kaare Christensen (Odense)
Rodger Elble (Springfield)
Alfonso Fasano (Roma)
Mark Hallett (Bethesda)
Paul Krack (Grenoble)
Jens Volkmann (Würzburg)

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