Moving Treatment Earlier
Disease Modification in Early PD

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- Speaking / Consultancy: Biotie, Roche, Biogen, Teva, Novartis, Jannsen, Abbvie,
Outline – Early / Prodromal

1. Setting the stage
   - Why does it exist? Why should we care?

2. How is Early Stage PD diagnosed?

3. Defining the Early stage
   - Prodromal PD criteria

4. How would we do this?
   - Selecting patients with Early PD
II. Non-Motor first

Stage 1
- dorsal motor, olfactory
- peripheral same time? Earlier?

Stage 2
- coeruleus, sub-ceruleus complex
  (function in sleep, mood)

Stage 3 – SNpc finally!
- motor symptoms (?)

Stages 4-6 - cortical involvement
- may have early presentation?

1. PD is not a SN disease!
2. PD may start with non-motor features
   (they can have redundancy too!)
Early PD – What to call it?
Why care?

Preclinical (no symptoms)

Prodromal

Clinical PD

Wow! But how?
How can we Pick up these Early stages
The Markers – Many!!

- **Established (>2 prospective studies)** ALL CLINICAL
  - Olfaction
  - RBD
  - Autonomic – **constipation**, urinary, erectile, orthostatic
  - Depression, Anxiety
  - Subtle Motor loss

- **Good evidence (1-2 prospective studies and makes sense)**
  - Color vision
  - **SN ultrasound**
  - Whole-Brain PET / SPECT
  - **Tissue Biopsy** (new!)
  - *(Dopaminergic PET)*

- **Likely (studies in high-risk groups)**
  - MRI
  - MIBG Sintrigraphy
Some Key Ones

• Olfaction: Evidence! **7 Prospective Studies**

• RR estimates consistent – median = **4-5**
  – Higher than many clinical markers

• Note: Dementia too (DLB >> AD)

• Testing - Easy
Constipation – Lead Time!

• Evidence very strong – 6 prospective studies
• Relative Risk low (2.5)
  – Predictive Value low
• Lead time – very long?
  – Some studies >20 years
  – How long is prodromal PD??????
    • Is constipation a risk factor?
      – Microbiome studies
      – Synuclein spread from gut – exposure time?
Power of RBD

1. Evidence strong (12 center study:)

2. Long term – high!

MOST RBD have prodromal PD – Implications ++
Conventional ‘Biomarkers’
Gradually Catching Up

• The Obvious one. ..
• Direct measure of SNpc
  – Should work!
• 2017: PARS
  – Hyposmics
  – <65% - 14/23
  – >80% - 4/135
• RR = 20
• Cost: secondary screen
Newer Markers:
Can we use MRI in Prodromal Disease?

• MRI – “Swallow Tail’ Sign = Nigrosome 1
  (Black-white-black to all-black)
• Lost in 92% of PD
• 1/35 controls
• 10/13 RBD
• Confirmed in Korean study (abstract)
• If there in most RBD, then prodromal?

DeMarzi, Ann Neurol, 2016
New Frontier: Tissue Diagnosis during Life

• Submandibular Salivary gland
  – 8/9 idiopathic RBD had positive biopsy

• Skin – **Simple** Punch Biopsy
  – 20/25 (80%) Early PD positive
  – 10/18 (56%) idiopathic RBD

• Trials using synuclein: Tissue as the diagnostic confirmation?


MDS task force on Definition of PD

Time to Redefine PD? Introductory Statement of the MDS Task Force on the Definition of Parkinson’s Disease

Daniela Berg, MD, Ronald B. Postuma, MD, MSc, Bastiaan Bloem, MD, PhD, Piu Chan, MD, PhD, Bruno Dubois, MD, PhD, Thomas Gasser, MD, Christopher G. Goetz, MD, Glenda M. Halliday, PhD, John Hardy, PhD, Anthony E. Lang, MD, FRCPC, Irene Litvan, MD, Kenneth Marek, MD, José Obeso, MD, PhD, Wolfgang Oertel, MD, C. Warren Olanow, MD, FRCPC, Werner Poewe, MD, Matthew Stern, MD, and Günther Deuschl, MD

MDS Research Criteria for Prodromal Parkinson’s Disease

Daniela Berg, MD, Ronald B. Postuma, MD, MSc, Charles H. Adler, MD, PhD, Bastiaan R. Bloem, MD, PhD, Piu Chan, MD, PhD, Bruno Dubois, MD, PhD, Thomas Gasser, MD, Christopher G. Goetz, MD, Glenda Halliday, PhD, Lawrence Joseph, PhD, Anthony E. Lang, OC, MD, FRCPC, Inga Liebelt-Scarfone, PhD, Irene Litvan, MD, Kenneth Marek, MD, José Obeso, MD, PhD, Wolfgang Oertel, MD, C. Warren Olanow, MD, FRCPC, Werner Poewe, MD, Matthew Stern, MD, and Günther Deuschl, MD

MDS Clinical Diagnostic Criteria for Parkinson’s Disease

Ronald B. Postuma, MD, MSc, Daniela Berg, MD, Matthew Stern, MD, Werner Poewe, MD, C. Warren Olanow, MD, FRCPC, Wolfgang Oertel, MD, José Obeso, MD, PhD, Kenneth Marek, MD, Irene Litvan, MD, Anthony E. Lang, OC, MD, FRCPC, Glenda Halliday, PhD, Christopher G. Goetz, MD, Thomas Gasser, MD, Bruno Dubois, MD, PhD, Piu Chan, MD, PhD, Bastiaan R. Bloem, MD, PhD, Charles H. Adler, MD, PhD, and Günther Deuschl, MD
MDS Prodromal Criteria
Calculating Probability

<table>
<thead>
<tr>
<th>Risk markers</th>
<th>LR + (male)</th>
<th>LR - (female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>1.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Regular Pesticide Exposure</td>
<td>1.5</td>
<td>n/a</td>
</tr>
<tr>
<td>Occupational Solvent Exposure</td>
<td>1.5</td>
<td>n/a</td>
</tr>
<tr>
<td>Non-use of Caffeine</td>
<td>1.35</td>
<td>.88</td>
</tr>
<tr>
<td>Smoking</td>
<td>n/a</td>
<td>.45</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.25</td>
<td>n/a</td>
</tr>
<tr>
<td>Never smoker</td>
<td>n/a</td>
<td>0.8</td>
</tr>
<tr>
<td>Former smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sibling had PD with age onset</td>
<td>7.5</td>
<td>n/a</td>
</tr>
<tr>
<td>Any other first degree relative with PD</td>
<td>2.5</td>
<td>n/a</td>
</tr>
<tr>
<td>Known gene mutation</td>
<td>see Table SII</td>
<td>n/a</td>
</tr>
<tr>
<td>Substantia Nigra Hyperechogenicity</td>
<td>4.7</td>
<td>0.45</td>
</tr>
</tbody>
</table>

**Prodromal Markers**

<table>
<thead>
<tr>
<th>Markers</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polysomnogram-proven RBD or Positive RBD screen questionnaire</td>
<td>130</td>
<td>0.62</td>
</tr>
<tr>
<td>with &gt;80% specificity</td>
<td>2.3</td>
<td>0.76</td>
</tr>
<tr>
<td>Dopaminergic PET/SPECT clearly abnormal</td>
<td>40</td>
<td>0.65</td>
</tr>
<tr>
<td>(e.g. &lt;65% normal, 2 SD below mean)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible subthreshold parkinsonism (UPDRS &gt;3 excluding action</td>
<td>10</td>
<td>0.7</td>
</tr>
<tr>
<td>tremor) or Abnormal Quantitative Motor Testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olfactory loss</td>
<td>4.0</td>
<td>0.43</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Excessive Daytime Somnolence</td>
<td>2.2</td>
<td>0.88</td>
</tr>
<tr>
<td>Symptomatic Hypotension</td>
<td>2.1</td>
<td>0.87</td>
</tr>
<tr>
<td>Severe Erectile Dysfunction</td>
<td>2</td>
<td>0.90</td>
</tr>
<tr>
<td>Urinary dysfunction</td>
<td>1.9</td>
<td>0.90</td>
</tr>
<tr>
<td>Depression (+/- Anxiety)</td>
<td>1.8</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Means to mathematically calculate chance of Prodromal PD
- threshold = 80%
- **already** needs updating (history RBD = LR 50, OH = LR 6, tissue biopsy, etc!)
- We now have a way to formally define prodromal disease
The Next step: Neuroprotective Trials

Why move to prodromal?

1. **Early**
   - Time to Intervene

2. **Untreated**
   - the only large population of untreated remaining
How to find them – The numbers
Population-Screening - Olfaction

• PARS study – partially enriched (50% family)

Mailout = 9398 people

Respond = 4999

Hyposmic = 669

Scanned = 203

Abnormal = 23

PD = 14

Yield???
Scalable??
RBD – More optimistic

• ‘Test case’ Ad in small community newspaper – RBD1Q
  “Have you ever been told, or suspected yourself, that you seem to act out your dreams" while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?”

• Follow with interview (RA, reviewed)

• **Goal**: get high Positive Predictive Value
  – Minimize polysomograms (cost)

• 111 answered ➔ 40 positive ➔ 29 PSG

• 19/29 had RBD (63%), 80% of these had prodromal PD
How to Plan a Prodromal trial
What do we need?

• Patient selection
  – Trials must be short (i.e. 2-3 years max)

• Outcomes
  – Must be robust (FDA, etc)
  – Best: prevent development of PD (and DLB)
    • Quantitative (quant. motor, cognitive, DAT scan) too
      – power not better
Baseline Risk in RBD population

a) Removing Antidepressant Triggered, Age ≥55

Overall = 8% per year
Can we do better? Add more predictors

a) Olfaction

b) Color Vision

c) Mild Motor Dysfunction (≥2 of 4 abnormal)

d) Autonomic Dysfunction (≥2 of 4 abnormal)

HR=3.3, p=0.002

HR=2.5, p=0.006

HR=3.7, p<0.001

HR=1.34, p=0.37

Postuma, Neurology, 2015
So, is a trial practical? - Yes!

### Hypothetical:

**2-year**
(w. 2 year accrual = 3 yrs.)

#### Definitive Endpoint
- Conversion to PD/DLB
- time to event analysis

#### Categorical Endpoint
80% power, p<0.05

#### 3 Different Effectiveness Assumptions

<table>
<thead>
<tr>
<th>Baseline (no stratification)</th>
<th>30</th>
<th>134</th>
<th>47</th>
<th>423</th>
<th>199</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;55, no antidepressant trigger AND Abnormal:</td>
<td>35</td>
<td>118</td>
<td>41</td>
<td>374</td>
<td>166</td>
</tr>
</tbody>
</table>

| Olfaction | 44 | 98 | 33 | 311 | 125 |
| Color vision | 49 | 90 | 30 | 286 | 108 |
| Motor (2/4) | 65 | 72 | 23 | 234 | 73 |

**Binomial Probability Estimate - (50% reduction in proportion)**

Time to event - [http://hedwig.mgh.harvard.edu/sample_size/time_to_event/para_time.html](http://hedwig.mgh.harvard.edu/sample_size/time_to_event/para_time.html)

Binomial - [http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html](http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html)
Do we have a trial population?

Unpublished data
- RBD study Group
- 24 centers

Risk = 6.3% per year
Do we have a trial population?

Unpublished data
- RBD study Group
- 24 centers

N = 1288
Summary

• Prodromal Disease can now be diagnosed
  – Clinical Markers best right now
  – Imaging / Tissue catching up
  – Encapsulated in criteria – can calculate risk

• Ultimate Payoff = neuroprotective trials
  – Neuroprotective trials are ready (RBD)
Final thought: Is Prodromal Trial ‘worth it’?

RCT will be done in clinical PD
One of two things will happen. ..

Success!
Response: Wonderful!
Can we expand indication / population?!

Failure
Response: Maybe we were too late?
did we miss the opportunity to intervene?

TRIAL IN PRODROMAL PD
(another company?)

If we will try anyway, why wait?

TRIAL IN PRODROMAL PD
(another company?)
Thank-you!

Questions? Comments?
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