Pre-motor Parkinson’s Disease Can be Diagnosed – Not Yet

Web Ross
VA Pacific Islands Health Care System
Ground Rules

- Focus of pre-motor diagnostic strategies will be on **sporadic PD**
- The setting for discussions of pre-motor PD diagnosis will be the **general population** as opposed to special populations such as those with family history.
Does a pre-motor phase of PD exist?

Synuclein pathology in gut

Striatal dopamine

4 to > 13 Years

Diagnosis
What are the pre-motor symptoms

- Impaired olfaction
- Disorders of sleep
  - REM sleep behavior disorder
  - Excessive daytime sleepiness
- Slow reaction time
- Autonomic abnormalities
  - Constipation
  - Prolonged QT interval
- Depression / Cognitive impairment
Olfactory dysfunction in the HAAS

Age adjusted PD incidence/10,000 p-ys by quartile of odor identification among 2263 men at risk
Age adjusted PD incidence / 10,000 p-ys by bowel movement frequency

PD incidence / 10,000 P-Ys

Bowel movements per day

<1 1 2 >2

18.9 7.9 5.4 3.9

P=0.005 for trend
Excessive daytime sleepiness (EDS)

Age adjusted PD incidence / 10,000 P-Ys among 3078 men aged 71 to 91 years in the HAAS free of PD at baseline (1991)

* P = 0.004
Reaction time testing

- There is significant prolongation of both simple and choice reaction times in Parkinson’s disease. This may reflect slowness in motor readiness as well as execution.

- Prolongation of reaction time may be associated with pathology in the gain setting nuclei in the brainstem (Braak stage 2)

% with Lewy bodies by quartiles of Choice reaction time measured approximately 2.2 years prior to death

Age adjusted test for trend: $P = 0.019$
PD incidence/10,000 person-years by number of early symptoms present

- Excessive Daytime Sleepiness
- Poor olfaction (bottom 20th percentile)
- Slow reaction time (slowest 20th percentile)
- <1 bowel movement/day

\[ P=0.009 \text{ Trend} \]

Number of symptoms

<table>
<thead>
<tr>
<th>Number of symptoms</th>
<th>PD Incidence</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>9/1087</td>
</tr>
<tr>
<td>1</td>
<td>8/582</td>
</tr>
<tr>
<td>2</td>
<td>2/166</td>
</tr>
<tr>
<td>&gt;= 3</td>
<td>2/24</td>
</tr>
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</table>
Positive test (≥ 3 pre-motor symptoms) for pre-motor PD

Negative test: < 3 symptoms
Positive test (≥ 3 pre-motor symptoms) for pre-motor PD

Negative test: < 3 symptoms

Positive test: ≥ 3 symptoms
Radiotracer Imaging for pre-motor PD diagnosis

- Nigral cell loss predates motor manifestations of PD by many years, so radiotracer imaging of the nigrostriatal dopaminergic system should show abnormalities prior to diagnosis.
- 10 to 15% of early PD have normal scans –
- There is discordance between imaging and clinical markers in that limit usefulness as a marker of progression.
- DAT-SPECT has been used along with hyposmia in relatives of PD.
- Abnormal DAT binding in asymptomatic LRRK2 mutation carriers.
- Sensitivity, specificity, predictive values are unknown in the general population.
Diagnostic accuracy of TRODAT SPECT imaging in early PD (Chou et al, 2004)

Sensitivity = 79%; Specificity = 92%

<table>
<thead>
<tr>
<th>% PD prevalence</th>
<th>Neg. PV</th>
<th>Pos. PV</th>
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<tbody>
<tr>
<td>50</td>
<td>0.81</td>
<td>0.91</td>
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<tr>
<td>25</td>
<td>0.93</td>
<td>0.77</td>
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<tr>
<td>10</td>
<td>0.98</td>
<td>0.52</td>
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<tr>
<td>5</td>
<td>0.99</td>
<td>0.34</td>
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<tr>
<td>2</td>
<td>0.99</td>
<td>0.17</td>
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<tr>
<td>1</td>
<td>0.99</td>
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Radiotracer Imaging for pre-motor PD diagnosis

• Conclusions:
  – Clearly worthy of study
  – Too early to tell if useful for pre-motor diagnosis
Transcranial sonography for pre-motor diagnosis of PD

- Hyperechogenicity in 90% of PD patients
- Pathological correlate unknown
- Adequate bone window is age dependent and absent in 10%
- Sensitivity 91%, specificity 82%, positive predictive value 93% for differentiating PD from atypical parkinsonian in population of early parkinsonian subjects
- Longitudinal studies of pre-motor subjects in general population are lacking
- Conclusions:
  - May assist with differential diagnosis
  - Not a useful tool for pre-motor diagnosis yet.
Pre-motor symptoms (constipation, hyposmia, slow reaction time, EDS) plus imaging assuming 100% sensitivity and specificity for imaging

<table>
<thead>
<tr>
<th># symptoms</th>
<th>% of sample</th>
<th>% who get PD</th>
<th>% who do not get PD</th>
<th># needed to scan for 1 case</th>
<th>Sample screened</th>
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<tbody>
<tr>
<td>0</td>
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<td>0.16</td>
<td>99.84</td>
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<tr>
<td>2</td>
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<td>99.71</td>
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<td>3911</td>
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<td>≥3</td>
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<td>2.16</td>
<td>97.84</td>
<td>47</td>
<td>3616</td>
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Conclusions

• There is a pre-motor period associated with symptoms and recognizable neuropathology
• Defining high risk for future PD is possible but identifying pre-motor PD in an individual is not
• A variety of imaging modalities show promise but predictive value is unknown in the general population
• More longitudinal population based studies needed before clinical application is possible