COGNITIVE IMPAIRMENT IN PARKINSON’S DISEASE

Dr. Maria Cruz Rodriguez-Oroz
Neurology and Neurosciences
Clinica Universidad de Navarra and CIMA
Pamplona

Outline
• Dementia in PD
• The spectrum of cognition in PD
• Executive dysfunction
• Mild cognitive impairment (MCI) and progression to dementia
• Normal cognition progression to MCI
• Pathophysiology of cognitive decline in PD
• Conclusiones

Dementia in PD

- Loss of autonomy → poor quality of life
- Risk of dementia is 6-8 higher than in general population
Mild Cognitive Impairment (MCI) in PD

"cognitive decline that is not normal for age but with essentially normal functional activities"

27-30% of PD patients

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Before MCI...?

Initial clinical manifestations of Parkinson’s disease: features and pathophysiological mechanisms

Lancet Neurol 2011

Cognitive manifestations

Cognitive deficits in PD range from "frontal executive dysfunction, which can be present in a mild form from early stages, to frank dementia in late stages."

are also seen at the time of diagnosis include sensory symptoms (eg. pain and tingling), hypotonia, sleep alterations, depression and anxiety, and abnormal executive, working memory-related functions.

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The spectrum of cognitive impairment in PD

- Normal Cognition
- Abnormal executive function and working memory
- Mild Cognitive Impairment
- Dementia
The spectrum of cognitive disorders in Parkinson’s disease: A data-driven approach

558 PD patients

Cluster 1: cognitively intact (19%)
Cluster 2: slowed mental speed, lower working memory and executive function (41%)
Cluster 3: slightly impaired overall cognition, performed slower and had lower scores in all cognitive domains than C 1 & 2. Below normal in everything but recognition memory (13%)
Cluster 4: C3 more severely affected plus severely affected in all cognitive domains including episodic memory (24%)
Cluster 5: very severely affected (dementia in most cases) (2.5%)

Dujardin et al, Mov Disord 2012

Non demented PD
Correlation between ¹⁸F-dopa uptake in right caudate and execution of the Tower of London and between left anterior putamen uptake and verbal working memory tasks

Cheesman et al, JNNP 2005

Caudate and Mesocortical DA depletion

EXECUTIVE DYSFUNCTION

Non demented PD
Correlation between frontal cognitive deficit and DAT in caudate

Müller et al, J Neural Transm 2000

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Cheesman et al, JNNP 2005

FAB and Brain perfusion

Gwee et al, J Neuror Sci 2008
Mild Cognitive Impairment (MCI) in PD

Diagnostic Criteria for Mild Cognitive Impairment in Parkinson’s Disease: Movement Disorder Society Task Force Guidelines

- Single domain:
  - executive function (most frequent)
  - attention/working memory
  - memory
  - language
  - visuospatial function
- Multiple domain

Mild Cognitive Impairment (MCI) in PD

- Heterogenous (number ad type of domains): attention, executive f., memory, language, visuospatial f.
- Most fre: Executive dysfunction
- Single vs multiple domain — 92-95% PD-MCI multidomain (MDS criteria) (Litvan et al. Mov Disord, Cholerton et al. Mov Disord 2014)
Evolution of MCI in PD

- No MCI: 37.20%
- MCI: 26-100%

NC → MCI → Dementia

ADVANCED PD

Longitudinal Assessment of the Pattern of Cognitive Decline in Non-Demented Patients with Advanced Parkinson’s Disease

>60 y.o.; PD > 10 years
70 patients: 32 PDNC and 38 PD-MCI (MD5 level II)
Follow-up: 31 months

Evolution of cognitive decline from MCI to dementia

PD-MCI converters (n=11)

PD-MCI non converters (n=15)

Predictors of dementia in PD-MCI (adjusted by age, education, duration of disease and gender):
- Copy of pentagona (MMSE): (p=0.032; OR=14.63; IC=1.25-171.12)
- Stroop words (p=0.005; OR=11.21; IC=1.03-1.42)
- Raven (p=0.047; OR=1.29; IC=1.01-1.66)
- number of cognitive domains affected (p=0.029; OR=8.32; IC=1.24-56.58)
Evolution to MCI in PD

<table>
<thead>
<tr>
<th>CN-MCI</th>
<th>PROBABILITY OF CN TO MCI</th>
<th>EVOLUTION TO CN TO MCI</th>
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<tbody>
<tr>
<td>3 years</td>
<td>3.0%</td>
<td>Executive Function</td>
</tr>
<tr>
<td>4 years</td>
<td>24%</td>
<td>Attention</td>
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<td>5 years</td>
<td>20%</td>
<td>Memory</td>
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<td>6 years</td>
<td>4.4%</td>
<td>Global cognition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Semantic fluency</td>
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<tr>
<td></td>
<td></td>
<td>Memory</td>
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Mild Cognitive Impairment as a Risk Factor for Parkinson’s Disease Dementia

Midi Hoogland et al., 2017

<table>
<thead>
<tr>
<th>Variable</th>
<th>β coefficient</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>95% CI for OR</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>0.08</td>
<td>0.09</td>
<td>1.09 (1.01, 1.18)</td>
<td>1.09 (1.01, 1.18)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.26</td>
<td>0.28</td>
<td>0.12 (0.02, 0.2)</td>
<td>0.12 (0.02, 0.2)</td>
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<td>Education</td>
<td>0.20</td>
<td>0.20</td>
<td>1.01 (1.01, 1.01)</td>
<td>1.01 (1.01, 1.01)</td>
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<tr>
<td>PD-MCI</td>
<td>0.20</td>
<td>0.20</td>
<td>1.01 (1.01, 1.01)</td>
<td>1.01 (1.01, 1.01)</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.67</td>
<td>0.67</td>
<td>1.01 (1.01, 1.01)</td>
<td>1.01 (1.01, 1.01)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.01</td>
<td>0.01</td>
<td>1.01 (1.01, 1.01)</td>
<td>1.01 (1.01, 1.01)</td>
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</tbody>
</table>

The distinct cognitive syndromes of Parkinson’s disease: 5 year follow-up of the CamPalGN cohort

Caroline H. Williams-Gray, Jonathan R. Evans, An Goris, Thomas Foltynie, Maria Bapr, Trevor W. Robbins, Carol Brayne, Bhaskar S. Kolschana, Daniel R. Weinberger, Stephen J. Sawcer and Roger A. Barker

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<tr>
<th>Variable</th>
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<th>P value</th>
<th>OR (95% CI)</th>
<th>95% CI for OR</th>
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</thead>
<tbody>
<tr>
<td>GSN-MCI</td>
<td>0.37</td>
<td>0.001</td>
<td>0.5</td>
<td>-</td>
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Dual hypothesis

Dopaminergic pathology; Cholinergic deficiency; White matter pathology; Gray matter degeneration; Vasculopathy; Alzheimer type pathology
Reduction in bilateral ventral striatum, right caudate and anterior cingulate in PPD vs PD.

Positive correlation between right caudate F-dopa and MMSE.

Ito et al. Brain 2002

Cholinergic deficit: AcE activity, MP4A PET, global cognition, executive function and attention

Correlation between cognitive tests in visuospatial and executive domain and cortical AChE in patients with PD with and without dementia.

Bohnen et al. J Neurol 2007
FDG-PET

Huang et al. Neurology 2008

Eckert 2007

Obeso MJi 2017
Teuleo et al, 2016

No differences between MCI single domain and patients with PDD patients showed large areas (occipito-parietal/ventral) of coincident hypometabolism and atrophy which were surrounded by areas of reduced FDG uptake. In PD-MCI patients hypometabolism was the main feature. Hypometabolism and atrophy might represent two steps of the same process initiated with a reduction of cortical glucose uptake evolving towards a decrease in grey matter volume, which appears to expand in an exocentric pattern as cognitive decline progresses.
Conclusions

• There is a spectrum of cognitive decline from normal cognition to dementia
• MCI is risk factor for dementia but...
• Current MCI in PD is an heterogeneous entity: different subtypes have different risk of dementia
  – DCL multidomain
  – Posterior cortical functions (visuospatial, memory)
  – Semantic fluency
  – Executive deficits. (Dual hypothesis)
• Different pathological mechanisms involved (LB, AD, AChE, DA etc) probably account for the different cognitive deficits and evolution