Parkinson Disease
Motor aspects

XXI World Congress of Neurology
Vienna, Austria, 21-26 September 2013

W. POEWE
Dept. of Neurology
Innsbruck Medical University

MEDIZINISCHE UNIVERSITÄT INNSBRUCK
TOPICS

* CARDINAL MOTOR FEATURES OF PD
* LD-RELATED MOTOR COMPLICATIONS
* MOTOR ASYMMETRY IN PD
What is Parkinson’s disease?

- **a clinical syndrome**
  * defined by the presence of cardinal motor features

- **a neuropathological entity**
  * defined by α-synuclein positive neuronal cytoplasmic (Lewy bodies) and axonal (Lewy neurites) inclusions and cell loss in the SNc
PDS BRC Criteria for Idiopathic Parkinson’s Disease
Definition of a Parkinsonian Syndrome

Bradykinesia,

plus one of

– Rigidity
– 4 - 6 Hz rest tremor
– Postural instability, not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

PDS BRC = Parkinson’s Disease Society Brain Research Center.
CLINICAL FEATURES OF BRADYKINESIA IN PD

- Bradykinesia = reduced speed of movement
- Hypokinesia = reduced and decrementing movement amplitude
- Akinesia = dysfunctional movement initiation
Total nigral age-adjusted count vs Symptom Duration (Fearnley and Lees, Brain 1991)

% of neuronal profiles left

Total nigral age-adjusted count vs Symptom Duration (Duyckaerts et al, 2005)

density of neurones in % of controls

\[ \text{density} = 10(1.86 - 0.83 \times \text{duration of the disease}) \]

\[ r = 0.7, p = 0.0003 \]
Asymmetric reduction of putaminal $[^{18}\text{F}]$Dopa uptake in PD
Correlations of motor symptoms and striatal Dopa PET uptake in Parkinson’s disease

Vingerhoets et al., Ann Neurol 1997
$[^{18}F]Dopa$ PET in PD risk subjects - correlation with UPDRS motor score

$r^2 = 0.48; p=0.002$
**PDS BRC Criteria for Idiopathic Parkinson’s Disease**

**Supportive Prospective Criteria**

- Unilateral onset
- Persistent asymmetry affecting side of onset most
- Rest tremor present
- Progressive disorder
- **Excellent response (70% - 100%) to levodopa**
- Severe levodopa-induced chorea
- Levodopa response for five years or more
- Clinical course of ten years or more

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NON-DOPAMINERGIC MOTOR SYMPTOMS IN PD?

* Posture, gait and balance
  postural instability
  falls
  freezing
  camptocormia
  trunk lateroflexion
  deformities of the hands and feet

* Speech problems
  dysarthria
  hypophonia
  palilalia

* Dysphagia
MOTOR COMPLICATION RATES WITH INITIAL L-DOPA-THERAPY

Retrospective uncontrolled studies 50 - 80 %
(Poewe et al, 1986) after 5 - 6 yrs

Community-based studies 30 - 40 %
(Schrag et al, 2000) after 5 yrs

Young-onset PD 90 % after 5 yrs
(Quinn et al, 1987; Schrag et al, 1998)

RCT’s 16 % after 9 mths
(PSG 2000; Whone et al, 2003; ELLDOPA) 30 - 40 % after 2 yrs
LD-RELATED MOTOR COMPLICATIONS IN PD

MOTOR RESPONSE FLUCTUATIONS
- wearing-off
- early morning akinesia
- random ON-OFF

LD-INDUCED DYSKINESIAS (LID’S)
- on-period chorea
- off-period dystonia
- biphasic dyskinesias
The Short Duration Response

Tolosa et al, 1975
Protein load effect on levodopa absorption

- 100 mg Benserazide p.o.
- 125 mg levodopa p.o.
- 60 mg milk protein p.o.

Graph showing plasmalevel (ng/ml) over time (hours) with different doses.
Beginning of Dose Difficulties

"Delayed On"

"ON"

"Off"

L-Dopa Dosing

"No On" Phenomenon (Dose Failure)

"ON"

"Off"

L-Dopa Dosing
Mechanisms of wearing-off
- Effect of protein loading on LD uptake -

Inhibition of L-[18F]Fluorodopa Uptake into Human Brain by Amino Acids Demonstrated by Positron Emission Tomography

K. L. Leenders,* W. H. Poewe,† A. J. Palmer,* D. P. Brenton,‡ and R. S. J. Frackowiak*

<table>
<thead>
<tr>
<th>Clinical pattern</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wearing-off</td>
<td>levodopa - t 1/2 pre-synaptic storage</td>
</tr>
<tr>
<td>Delayed-on</td>
<td>gastric emptying intestinal absorption</td>
</tr>
<tr>
<td>Dose-failures (No-on)</td>
<td>gastric emptying intestinal absorption</td>
</tr>
<tr>
<td></td>
<td>BBB-transport</td>
</tr>
<tr>
<td>Random ON-OFF</td>
<td>striatal pharmacodynamic changes</td>
</tr>
</tbody>
</table>
DRUG-INDUCED DYSKINESIAS IN PARKINSON’S DISEASE

ON-PERIOD DYSKINESIAS („INTERDOSE“)
- phasic (choreic) limb movements
- dystonic craniocervical movements
- more pronounced on side initially affected by PD

BIPHASIC DYSKINESIAS
- at onset or wearing-off of clinical benefit from a dose
  of levodopa (or both)
- mix of phasic and dystonic movements („mobile dystonia“)

OFF-PERIOD DYSTONIA
- most often distal limb (feet)
- painful
Discontinuous drug delivery and pulsatile stimulation of dopamine receptors

Conventional levodopa

Activated
Unactivated

Normal

Activated
Unactivated

PD (untreated)

Conventional levodopa

Activated
Unactivated

Nigrostriatal neurons degenerate

Substantia nigra

Striatum

Conventional levodopa
Mechanisms of wearing-off: Dose-dependent fluctuations in synaptic DA-concentrations

Baseline 1 hour after oral levodopa 4 hours after oral levodopa

De la Fuente-Fernández et al, 2001
Progressive degeneration of dopamine neurones leads to reduced dopamine storage capacity in the striatum

Fluctuations in plasma levodopa levels because of the drug’s short half-life can no longer be ‘buffered’

Pulsatile stimulation of striatal dopamine receptors

Downstream dysregulation of genes, proteins and second messenger systems

Altered basal ganglia firing patterns

Motor complications
L-DOPA-INDUCED DYSKINESIAS IN PD
- Risk factors -

• Well established
  - Younger age at onset
  - Treatment duration
  - LD-dose

• Less well established
  - Disease duration
  - Disease severity
Maladaptive Plasticity of Serotonin Axon Terminals in Levodopa-Induced Dyskinesia

Daniella Rylander, PhD, Martin Parent, PhD, Sean S. O’Sullivan, MB, MRCPI, Sandra Dovero, PhD, Andrew J. Lees, MD, FRCP, Erwan Bezard, PhD, Laurent Descarries, MD, FRCP(C), and M. Angela Cenci, MD, PhD

ANN NEUROL 2010;68:619–628
The enigma of motor asymmetry in Parkinson’s disease
Hoehn and Yahr Scale

1: Unilateral involvement only, usually with minimal or no functional disability

2: Bilateral or midline involvement without impairment of balance

3: Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent*

4: Severely disabling disease; still able to walk or stand unassisted

5: Confinement to bed or wheelchair unless aided

* Stage 3 is a summary of the author's original, more narrative description
Asymmetric reduction of putaminal $[^{18}\text{F}]$Dopa uptake in PD

Proband

Parkinson-Krankheit
Persistent asymmetry of nigrostriatal dysfunction (FP-CIT-SPECT) in PD

Djaldetti et al, Mov Disord 2010
Asymmetry of substantia nigra neuronal loss in Parkinson's disease and its relevance to the mechanism of levodopa related motor fluctuations.

PA KEMPSTER,† W R G GIBB,† G M STERN,* A J LEES†

From the Department of Neurology, Middlesex Hospital* and Department of Neuropathology, National Hospital for Nervous Diseases, Maida Vale,† London, UK
WHY ARE PD MOTOR SIGNS ASYMMETRIC?

A

Initiation of neurodegeneration

Number of dopaminergic cells

SN right

SN left

Years

Critical number for symptom appearance

B

Initiation of neurodegeneration

Number of dopaminergic cells

SN right

SN left

Years

Critical number for symptom appearance

Djaldetti und Melamed, 2006
HYPOTHETICAL MECHANISMS UNDERLYING MOTOR ASYMMETRY IN PD

ANATOMICAL
- R/L differential in SN neuronal count
- hemispheric asymmetry of motor circuits

FUNCTIONAL
- asymmetric dopamine concentrations
- asymmetric dysfunction of blood-brain-barrier
- asymmetric progression of synuclein pathology
- effects of hemispheric dominance

GENETIC
- genetically determined lateralised vulnerability and/or organisation of motor circuits
HEMISPHERIC ASYMMETRY AND PD
- Anatomical and functional findings in healthy subjects -

* **MR Volumetry** – Basal ganglia volume L > R
  (Murphy et al, 1992)

* **DAT-SPECT** – greater tracer binding in L Striatum
  (Dyck et al, 2002)

* **Neurotransmitter levels** – striatal DA-concentrations L > R
  (Glick et al, 1982)
Correlation between R-Handedness and putaminal F-DOPA-$K_i$ ($N=20$)

De la Fuente-Fernández et al, 2000
Neuroprotective effects of prior limb use in 6-hydroxydopamine-treated rats: possible role of GDNF

Ann D. Cohen,*† Jennifer L. Tillerson,† Amanda D. Smith,* Timothy Schallert†‡ and Michael J. Zigmond*
Improvement of long duration response dependent on L-Dopa and motor activity (greater improvement in dominant hand)
Handedness Correlates with the Dominant Parkinson Side: A Systematic Review and Meta-analysis

Anouk van der Hoom, BSc,¹* Huibert Burger, MD, PhD,²,³ Klaus L. Leenders, MD, PhD,¹ and Bauke M. de Jong, MD, PhD¹

¹Department of Neurology, University Medical Center Groningen, University of Groningen, The Netherlands
²Interdisciplinary Center for Psychiatric Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands
³Department of Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands

Mov Disord 2012;27:206-10

• 10 studies with sufficient information on handedness and motor asymmetry

• N = 4405 Patients (92.1% R-Handed)

• R-Handed (N=4057)
  - 59.5 % R > L
  - 40.5 % L > R

• L-Handed (N=348)
  - 40.8 % R > L
  - 59.2 % L > R
N = 68 patients

- UK PDSBB Criteria
- symptom onset > 50 a
- positive DAT-SPECT (ß-CIT)
- positive LD response
- mean age 63 a
- mean disease duration 2 a

- UPDRS III Score „ON“
- Edinburgh Handedness Inventory
- side of symptom onset
- UPDRS III AI
Template-based ROI-Analysis

A
ROIs in MRI template space

B
DAT SPECT and ROIs in MRI template space

C
Inverse projection of ROIs onto the single DAT SPECT

Scherfler et al, Brain 2012
Inclusion criteria:
Diagnosis according to UK PDSBB Criteria
Age > 50 yrs
Levodopa responsiveness
Decreased striatal DAT binding (SPECT)

Exclusion criteria:
Clinical signs of atypical parkinsonism
Basal ganglia lesions in CT/MRI

<table>
<thead>
<tr>
<th></th>
<th>PD-LEFT patients [n = 49* (72%)]</th>
<th>PD-RIGHT patients [n = 19 (28%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female/male</td>
<td>19/30</td>
<td>6/13</td>
</tr>
<tr>
<td>Age at DAT SPECT (years)</td>
<td>62.2 ± 7.4</td>
<td>63.9 ± 6.3</td>
</tr>
<tr>
<td>Disease duration until DAT SPECT (years)</td>
<td>2.2 ± 1.5</td>
<td>2 ± 1.5</td>
</tr>
<tr>
<td>UPDRS motor score</td>
<td>20 ± 7.1</td>
<td>30.2 ± 9.9**</td>
</tr>
<tr>
<td>Time period between DAT SPECT and UPDRS (years)</td>
<td>0.8 ± 1.2</td>
<td>1 ± 1.3</td>
</tr>
<tr>
<td>UPDRS asymmetry subscorea</td>
<td>7.2 ± 3.4</td>
<td>6 ± 3.3</td>
</tr>
<tr>
<td>Right-side</td>
<td>41 (83.7)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Left-side</td>
<td>8 (16.3)</td>
<td>17 (89.5)</td>
</tr>
</tbody>
</table>

L-HEMISPHERIC PREDOMINANCE OF NIGROSTRIATAL DYSFUNCTION IN PD

Scherfler et al, Brain 2012
MOTOR ASPECTS OF PD
- Summary -

* Close correlation between bradykinesia and striatal dopaminergic denervation

* Postural instability and motor blocks (FOG) of advanced PD probably due to additional dysfunction in non-dopaminergic pathways

* LD-related motor complications reflect pharmacokinetics of levodopa and „maladaptive“ neuroplasticity

* Asymmetry of motor signs in PD partially related to hemispheric dominance
Effects of laterality on degree of loss of dexterity
- Haaxma et al, Neuroscience 2010 -

Dexterity test score (mean)

<table>
<thead>
<tr>
<th></th>
<th>Dominant hand</th>
<th>Non-dominant hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS N=48</td>
<td>9.6</td>
<td>10.0</td>
</tr>
<tr>
<td>PD-LEFT N=103</td>
<td>17.1</td>
<td>11.7</td>
</tr>
<tr>
<td>PD-RIGHT N=83</td>
<td>10.8</td>
<td>20.2</td>
</tr>
</tbody>
</table>

*Δ = 55%
\(p = 0.008\)

Performance of more-affected hand
\(p < 0.001\)

Performance of less-affected hand
\(p = 0.33\)
Table 2. Topography of L-Dopa-Induced Dystonia in Parkinson's Disease (n = 56)

<table>
<thead>
<tr>
<th>Body Area Involved</th>
<th>Off-Period (n = 46)</th>
<th>Biphasic (n = 7)</th>
<th>Peak-Dose (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot</td>
<td>46</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Proximal leg</td>
<td>5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Ipsilateral arm</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Trunk</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Face/neck</td>
<td>1</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

Poewe et al, Ann Neurol 1988
Motor loop somatotopic organisation

Rodriguez-Oroz et al, Lancet Neurol 2009
Maladaptive Plasticity of Serotonin Axon Terminals in Levodopa-Induced Dyskinesia

Daniella Rylander, PhD,1 Martin Parent, PhD,2 Sean S. O’Sullivan, MB, MRCPI,3 Sandra Dovero, PhD,4 Andrew J. Lees, MD, FRCP,3 Erwan Bezdard, PhD,4 Laurent Descaries, MD, FRCP(C),5,6 and M. Angela Cenci, MD, PhD1

ANN NEUROL 2010;68:619–628
HYPOTHETICAL MECHANISMS UNDERLYING MOTOR ASYMMETRY IN PD

ANATOMICAL
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FUNCTIONAL
- asymmetric dopamine concentrations
- asymmetric dysfunction of blood-brain-barrier
- asymmetric progression of synuclein pathology
- effects of hemispheric dominance

GENETIC
- genetically determined lateralised vulnerability and/or organisation of motor circuits
Genetic determinance of laterality?
- Evidence from twin studies -

- F-DOPA-PET studies in monogygotic PD twins show lateralised signal reductions in asymptomatic twins

- $^{18}$F-DOPA-PET in 6 monogygotic twin pairs show concordance for lateralised symptoms in 5 of 6 (Piccini, personal communication)

- Discordant laterality in 4 of 7 monogygotic twin pairs (Chade, Mov Disord 2006)

- Inconsistent asymmetry in 7 patients from large Austrian VPS-35 family (4 R, 3 L) (Struhal, personal communication)
# L-HEMISPHERIC PREDOMINANCE OF NIGROSTRIATAL DYSFUNCTION IN PD

**Mean regional $[^{123}I]\beta$-CIT BP$_{ND}$**

<table>
<thead>
<tr>
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<th>PD-LEFT patients ($n = 49^{* * *}$)</th>
<th>PD-RIGHT patients ($n = 19$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left caudate</td>
<td>$7.2 \pm 1.9^{***}$</td>
<td>$7.5 \pm 1.5^{***}$</td>
</tr>
<tr>
<td>Right caudate</td>
<td>$7.4 \pm 1.9^{***}$</td>
<td>$6.6 \pm 1.5^{***}$</td>
</tr>
<tr>
<td>Left posterior putamen</td>
<td>$3.9 \pm 1.32^{**}$</td>
<td>$4 \pm 0.9^{***}$</td>
</tr>
<tr>
<td>Right posterior putamen</td>
<td>$5 \pm 1.4^{***}$</td>
<td>$3.6 \pm 0.8^{**,*;++}$</td>
</tr>
</tbody>
</table>

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<th>PD-RIGHT patients ($n = 19$)</th>
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<tbody>
<tr>
<td>Mean caudate</td>
<td>$7.3 \pm 1.8^{***}$</td>
<td>$7 \pm 1.6^{***}$</td>
</tr>
<tr>
<td>Mean posterior putamen</td>
<td>$4.5 \pm 1.2^{***}$</td>
<td>$3.8 \pm 0.9^{**<em>,</em>}$</td>
</tr>
<tr>
<td>Asymmetry index of caudate</td>
<td>$13.6 \pm 8.8^{***}$</td>
<td>$15.1 \pm 9.1^{***}$</td>
</tr>
<tr>
<td>Asymmetry index of posterior putamen</td>
<td>$23.2 \pm 16.5^{**,*;++}$</td>
<td>$13.8 \pm 8.1^{*}$</td>
</tr>
<tr>
<td>Ratio of caudate/posterior putamen left</td>
<td>$2 \pm 0.8^{**}$</td>
<td>$1.9 \pm 0.5^{**}$</td>
</tr>
<tr>
<td>Ratio of caudate/posterior putamen right</td>
<td>$1.6 \pm 0.6^{*,#}$</td>
<td>$1.9 \pm 0.6^{**}$</td>
</tr>
</tbody>
</table>

Scherfler et al, Brain 2012
Neuroprotective effects of prior limb use in 6-hydroxydopamine-treated rats: possible role of GDNF

Ann D. Cohen,*,† Jennifer L. Tillerson,† Amanda D. Smith,*, Timothy Schallert†,‡ and Michael J. Zigmond*
Clinical and imaging asymmetry index (AI)

UPDRS motor asymmetry index

\[
\frac{a - b}{\sqrt{2}}
\]

\(a, b \ldots\) R and L scores of UPDRS items 20-26

DAT asymmetry (%) caudate and posterior putamen

\[
\left[\frac{a - b}{a + b}\right] \times 2 \times 100
\]

\(a, b \ldots\) R and L putamen or caudate

Uitti et al., Neurology 2005; Zijlmans et al., 2007
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>% with asymmetry</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uitti et al, 2006</td>
<td>1277</td>
<td>46 %</td>
<td>UPDRS R-L ≥ 5</td>
</tr>
<tr>
<td>Stocchi et al, 2009</td>
<td>472</td>
<td>84 %</td>
<td>clinical</td>
</tr>
<tr>
<td>Barrett et al, 2010</td>
<td>1173</td>
<td>86.5 %</td>
<td>clinical</td>
</tr>
</tbody>
</table>
TOPICS

* CARDINAL MOTOR FEATURES OF PD
* LD-RELATED MOTOR COMPLICATIONS
* LD-INDUCED DYSTONIA
* MOTOR ASYMMETRY IN PD
Topography of parkinsonian initial symptoms and levodopa-induced dyskinesia in 20 patients with Parkinson’s disease
- Vidailhet et al, Neurology 1994 -

<table>
<thead>
<tr>
<th>Body area involved</th>
<th>Initial symptoms of parkinsonism</th>
<th>Levodopa-induced dyskinesia during the levodopa test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Onset-of-dose</td>
</tr>
<tr>
<td>Foot and lower limb</td>
<td>6</td>
<td>20 (dystonia)</td>
</tr>
<tr>
<td>Upper limb</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Trunk / Neck</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Face</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Why does OFF-period dystonia affect the foot?
PDS BRC Criteria for Idiopathic Parkinson’s Disease Supportive Prospective Criteria

- Unilateral onset
- Persistent asymmetry affecting side of onset most
- Rest tremor present
- Progressive disorder
- Excellent response (70% - 100%) to levodopa
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- Levodopa response for five years or more
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PDS BRC = Parkinson’s Disease Society Brain Research Center.
# Joint and Skeletal Deformities in Parkinsonism

<table>
<thead>
<tr>
<th>Deformity</th>
<th>PD (N=164)</th>
<th>MSA (N=19)</th>
<th>PSP (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatal limb deformities</td>
<td>12.8% (21)</td>
<td>26.3% (5)</td>
<td>5.3% (1)</td>
</tr>
<tr>
<td>Involuntary trunk flexion</td>
<td>12.2% (20)</td>
<td>26.3% (5)</td>
<td>5.3% (1)</td>
</tr>
<tr>
<td>Anterocollis</td>
<td>5.5% (9)</td>
<td>42.1% (8)</td>
<td>10.5% (2)</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>8.5% (14)</td>
<td>10.5% (2)</td>
<td>5.3% (1)</td>
</tr>
<tr>
<td>All deformities</td>
<td>33.5% (55)</td>
<td>68.4% (13)</td>
<td>26.3% (5)</td>
</tr>
</tbody>
</table>

Pts. with deformities vs. without
- younger age (60.4 vs. 68.6 yrs)
- earlier onset age (55 vs. 62 yrs)
- higher UPDRS (57 vs. 46)
- more frequent LD (70% vs. 50%)

Ashour and Jankovic, Mov Disord 2006
Axial deformities in Parkinson’s disease

- Lateral flexion of the trunk common in advanced PD

- Duvoisin und Marsden 1975, JNNP
  19 PD patients with lateral flexion of the trunk contralateral to initially affected side
  „Scoliosis of PD“
  few recent studies

Richer und Meige 1895
Lateral flexion of the trunk in PD
Lateral trunk flexion: quantitative assessment

WINKEL 1: 8,7°
WINKEL 2: 11°
WINKEL 3: 7,3°
WINKEL 4: 9,5°
# Lateral trunk flexion in PD
- a descriptive study -

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>99</td>
<td>33</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>68.2a (51-80)</td>
<td>66.2a (53-88)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>33w/66m</td>
<td>19w/14m</td>
</tr>
</tbody>
</table>
# Lateral trunk flexion in PD  
- a descriptive study -

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UPDRS III</strong></td>
<td>21</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>H&amp;Y</strong></td>
<td>2,4</td>
<td>-</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>27,4</td>
<td>29,2</td>
</tr>
<tr>
<td></td>
<td>(11 &lt;24)</td>
<td>(0 &lt;24)</td>
</tr>
<tr>
<td><strong>FOG</strong></td>
<td>6,5</td>
<td>0</td>
</tr>
<tr>
<td><strong>OH</strong></td>
<td>34</td>
<td>9</td>
</tr>
</tbody>
</table>
## Lateral trunk flexion in PD

- **Frequency** -

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 3^\circ$</td>
<td>32 %</td>
<td>3 %</td>
</tr>
<tr>
<td>$\geq 5^\circ$</td>
<td>13 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>
Lateral trunk flexion in PD
- Laterality -

Flexion towards most affected side 47%

Flexion away from most affected side 47.5%
Lateral trunk flexion in PD
- Correlations -

- Univariant analysis
  - Disease duration (p=0.004)
  - Presence of dyskinesias (p=0.005)

- Multivariant analysis
  - Disease duration (p=0.006)
Lateral trunk flexion in PD
- Correlations -

• No significant correlation with

  - Age (p=0.63)
  - UPDRS III (p=0.74)
  - Motor fluctuations (p=0.69)
  - Freezing (p=1.0)
  - OH (p=0.43)
  - Visual hallucinations (p=0.20)
  - MMSE (p=0.17)
# Axial deformities in PD

<table>
<thead>
<tr>
<th></th>
<th>Country</th>
<th>Number of patients with PD</th>
<th>Prevalence (%)</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Camptocormia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abe et al⁸</td>
<td>Japan</td>
<td>153</td>
<td>18%</td>
<td>45° TL flexion</td>
</tr>
<tr>
<td>Tiple et al⁹</td>
<td>Italy</td>
<td>275</td>
<td>7%</td>
<td>45° TL flexion</td>
</tr>
<tr>
<td>Lepoutre et al¹⁰</td>
<td>France</td>
<td>700</td>
<td>3%</td>
<td>TL flexion</td>
</tr>
<tr>
<td>Ashour and Jankovic¹</td>
<td>USA</td>
<td>164</td>
<td>12%</td>
<td>45° TL flexion</td>
</tr>
<tr>
<td><strong>Antecollis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ashour and Jankovic¹</td>
<td>USA</td>
<td>164</td>
<td>6%</td>
<td>&gt;45° neck flexion</td>
</tr>
<tr>
<td>Yamada et al¹⁰</td>
<td>Japan</td>
<td>126</td>
<td>6%</td>
<td>NA</td>
</tr>
<tr>
<td>Kashihara et al¹¹</td>
<td>Japan</td>
<td>252</td>
<td>6%</td>
<td>Neck flexion</td>
</tr>
<tr>
<td>Fujimoto¹²</td>
<td>Japan</td>
<td>131</td>
<td>5%</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Pisa syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bonanni et al¹³</td>
<td>Italy</td>
<td>1400</td>
<td>2%</td>
<td>&gt;15° lateral flexion</td>
</tr>
<tr>
<td><strong>Scoliosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baik et al¹⁴</td>
<td>Korea</td>
<td>97</td>
<td>33%</td>
<td>Radiograph (Cobb method)</td>
</tr>
<tr>
<td>Ashour and Jankovic¹</td>
<td>USA</td>
<td>164</td>
<td>9%</td>
<td>Lateral curvature</td>
</tr>
<tr>
<td>Grimes et al¹⁵</td>
<td>UK</td>
<td>103</td>
<td>60%</td>
<td>Clinical, radiography in 50%</td>
</tr>
<tr>
<td>Duvoisin and Marsden¹⁶</td>
<td>UK</td>
<td>21</td>
<td>91%</td>
<td>Clinical examination</td>
</tr>
<tr>
<td>Indo and Ando¹⁷</td>
<td>Japan</td>
<td>70</td>
<td>31%</td>
<td>Clinical examination</td>
</tr>
<tr>
<td>Serratrice and Schiano¹⁸</td>
<td>France</td>
<td>140</td>
<td>13%</td>
<td>Clinical then radiography</td>
</tr>
<tr>
<td>Sicard¹⁹</td>
<td>France</td>
<td>17</td>
<td>47%</td>
<td>NA</td>
</tr>
<tr>
<td>Onuaguluchi²⁰</td>
<td>UK</td>
<td>33</td>
<td>15%</td>
<td>NA</td>
</tr>
</tbody>
</table>

TL=thoracolumbar. NA=data not available.

Doherty et al, Lancet Neurol 2011
DYSTONIA IN UNTREATED P.D.
- Deformities of hands and feet -

J. M. Charcot, 1877; W.R. Gowers, 1888; F.H. Lewy, 1913; P. Gortvai, 1963
Axial deformities in Parkinson’s disease

„propensity to bend the trunk forward“

UPDRS III
28. Posture
0-normal erect
1-slightly stooped, could be normal for older person
2-definitely abnormal, mod. stooped, may lean to one side
3-severely stooped with kyphosis
4-marked flexion with extreme abnormality of posture
Extensor Muscle Myopathy in PD
- Possible causes -

(1) Primary Myopathy
   - Focal Myositis
   - Inclusion Body Myositis
   - Dystrophic Myopathy
   - Mitochondrial Myopathy

(2) Secondary Myopathy
   - Aging
   - Chronic stretch / overuse (flexor rigidity)
   - Underuse (bradykinesia)
Camptocormia: Definition

- Camptocormia (gr.: kamptos = bent; kormos = trunk)
  - Severe unfixed forward flexion of the thoracolumbar spine
    - Worsening with standing and walking
    - Abates when sitting or recumbent
  - Different etiologies reported
    - E.g. myasthenia, psychogenic, ALS, myositis, GBS, tardive, GTS, DAT…PD
Camptocormia in PD

„...the body being so bowed and the head so forward..as to oblige him to employ a stick..to force him more to upright posture..“
James Parkinson 1817

• First case series 1999

• More frequent in rigid-akinetic subtype
• Sub-acute or chronic
• Back pain common
• Prevalence 3-17%

Drawing of a patient with Parkinson’s disease and camptocormia (Bibliothèque Charcot); from Bloch et al. 2006

1Djaldetti et al 1999 2Doherty et al 2011
Preclinical reduction in striatal \([^{18}F]-\text{Fluorodopa}\) uptake

Control subject  Parkin mutation carrier

Khan NK, Scherfler C, Brooks DJ, Piccini P. 2004
# PRODROMAL MOTOR ABNORMALITIES IN PD-RISK GROUPS

<table>
<thead>
<tr>
<th>TYPE OF ABNORMALITY</th>
<th>COHORT TESTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait variability under challenge</td>
<td>LRRK2 mutation carriers ¹</td>
</tr>
<tr>
<td>Increased UPDRS scores</td>
<td>LRRK2 mutation carriers ², ³</td>
</tr>
<tr>
<td>Acceleration of static sway</td>
<td>Healthy subjects with SN hyperechogenicity ⁴</td>
</tr>
<tr>
<td>Unilateral reduced arm swing</td>
<td>Elderly subjects with SN hyperechogenicity ⁵</td>
</tr>
<tr>
<td>Finger tapping, purdue peg board, timed up-and-go</td>
<td>Idiopathic RBD ⁶, ⁷</td>
</tr>
</tbody>
</table>

What is Parkinson’s disease?

Parkinson’s disease (PD) - a clinicopathological entity

- **a clinical syndrome**
  * defined by the presence of cardinal motor features (BUT with many non-motor features!)

- **a neuropathological syndrome**
  * defined by α-synuclein positive neuronal cytoplasmic (Lewy bodies) and axonal (Lewy neurites) inclusions and cell loss in the SNc

- **a biomarker supported clinical syndrome?**
  * imaging
  * molecular (genomic, proteomic)
Classification of Parkinsonism

• Neurodegenerative parkinsonism
  – Idiopathic Parkinson’s disease (IPD)
    • Sporadic
    • Genetic
  – Atypical parkinsonian disorders

• Symptomatic parkinsonism
  – Drug-induced
  – Vascular parkinsonism
  – Basal ganglia lesions
  – Toxic (MPTP, CO, CN, MN)
  – Encephalitis
  – Frontal meningeoma

MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NPH = normal pressure hydrocephalus; SAE = subcortical arteriosclerotic encephalopathy.
Common errors in the diagnosis of PD

Relate to:

- Essential Tremor
- Atypical Parkinsonian disorders
  - Multiple system atrophy
  - Progressive supranuclear palsy
- Vascular parkinsonism

UKPDS brain Bank criteria
STEP 2: Exclusion criteria?

• History:
  • repeated strokes
  • head injury
  • neuroleptic treatment
  • sustained remission
  • Negative response to large doses of levodopa

• Systematic neurological exam
  • Supranuclear gaze palsy
  • Cerebellar signs
  • Early severe autonomic involvement
  • Early severe dementia
  • Babinski sign
  • strictly unilateral features after 3 yrs

Gibb and Lees JNNP 1988
# MOTOR PHENOTYPE IN YOUNG-ONSET PD

(Gibb and Lees, 1988)

## Median age at onset (yrs)
- **YOUNG-ONSET** (N=46): 38 (24-45)
- **OLD-ONSET** (N=52): 73 (70-90)

## Median duration (yrs)
- **YOUNG-ONSET** (N=46): 11 (1-34)
- **OLD-ONSET** (N=52): 6 (1-11)

## First symptom

<table>
<thead>
<tr>
<th>Symptom</th>
<th>YOUNG-ONSET</th>
<th>OLD-ONSET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest tremor</td>
<td>19 (41%)</td>
<td>33 (63%)</td>
</tr>
<tr>
<td>Difficulty walking</td>
<td>2 (4%)</td>
<td>17 (33%)</td>
</tr>
<tr>
<td>Stiff muscles</td>
<td>20 (43%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Slowness</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Stiffness and tremor</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Weakness</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

## Mean dose of L-Dopa (mg)
- **YOUNG-ONSET** (N=46): 590.8 (30)
- **OLD-ONSET** (N=52): 595.8 (12)

## Number of pts with dyskinesia
- **YOUNG-ONSET** (N=46): 29 (91%)
- **OLD-ONSET** (N=52): 9 (69%)

## Number of pts with dystonia
- **YOUNG-ONSET** (N=46): 11 (34%)
- **OLD-ONSET** (N=52): 0/13
Motor complication rates in the ELLDOPA Trial

Factors Predictive of the Development of Levodopa-Induced Dyskinesia and Wearing-Off in Parkinson’s Disease

C. Warren Olanow, MD, FRCPC,1,2*, Karl Kieburtz, MD, MPH,3 Olivier Rascol, MD, PhD,4 Werner Poewe, MD,5 Anthony H. Schapira, MD, DSc, FRCP, FMedsoc,6 Murat Emre, MD,7 Helena Nissinen, MD, PhD,8 Mika Leinonen, MSc,9 Fabrizio Stocchi, MD, PhD,2 for the Stalevo Reduction in Dyskinesia Evaluation in Parkinson’s Disease (STRIDE-PD) Investigators

Mov Disord 2013 (in press)

*for patients who did not get dyskinesia: dose at the end of study

for patients who got dyskinesia: pre-dyskinesia dose
Efficacious treatments for levodopa-related motor complications in PD

**MOTOR FLUCTUATIONS**
- DA-agonists (pramipexole, ropinirole, rotigotine, apomorphine, pergolide)
- L-Dopa (enteral infusions, rapid onset formulations)
- COMT inhibitors (entacapone, tolcapone)
- MAO-B inhibitors (rasagiline)
- DBS surgery (STN, GPi)
- Unilateral pallidotomy

**DYSKINESIAS**
- Amantadine
- DBS surgery (STN, GPi)
- Unilateral pallidotomy

DBS=deep brain stimulation; STN=subthalamic nucleus; GPi=Globus Pallidus pars interna

Fox et al, MDS Task Force 2011
Pharmacological management of motor fluctuations

• **Modify L-dopa delivery and pharmacokinetics**
  – Reduce inter-dose interval – increase dose frequency
  – Increase dose
  – Use sustained-release L-dopa
  – Add COMT inhibitor
  – Use intrajejunal infusions of L-dopa

• **Enhance striatal dopamine concentrations**
  – Use MAO-B inhibitors, e.g., rasagiline

• **Use dopamine agonists**
  – Oral agonists (non-ergot)
  – Transdermal (rotigotine)
  – s.c. (apomorphine)
Dyskinesias and motor fluctuations in a community-based study of PD
(Schrag et al, 2000)

RESULTS

* Dyskinesias in 28 % of the patients

* Motor fluctuations in 40 % of the patients

* Predictors for the evolution of motor fluctuations:
  - Disease duration
  - LD dose

* Predictors for the evolution of dyskinesias:
  - Duration of treatment
MPTP induces dystonia and parkinsonism

Clues to the pathophysiology of dystonia
Clues to the pathophysiology of dystonia

J.S. Perlmutter, MD; L.W. Tempel, MD; K.J. Black, MD; D. Parkinson, PhD; and R.D. Todd, PhD, MD

Article abstract—The pathophysiology of dystonia is unclear, but several clues implicate striatal dopamine dysfunction. In contrast, the causal relationship between striatal dopamine deficiency and parkinsonism is well defined. We now suggest that parkinsonism or dystonia may occur following striatal dopamine deficiency. Baboons treated with intracarotid 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) developed transient hemidystonia prior to hemiparkinsonism. The day after MPTP treatment, most animals had spontaneous ipsilateral turning. Within a few days, all developed contralateral hemidystonia, with the arm and leg extended and externally rotated. This transient dystonia preceded hemiparkinsonism with flexed posture, bradykinesia, and postural tremor that persisted for up to 1.5 years. Dystonia corresponded temporally with a decreased striatal dopamine content and a transient decrease in D₂-like receptor number. The time course of dystonia and parkinsonism is analogous to lower limb dystonia as the first, frequently transient, symptom of Parkinson’s disease in humans. The association of striatal dopamine deficiency with dystonia and parkinsonism implies that other factors influence clinical manifestations.
DYSTONIA IN UNTREATED PD
(N = 30 from 3 series*)

<table>
<thead>
<tr>
<th>Dystonia preceding PD</th>
<th>21 / 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonia - PD latency &lt; 10 yrs.</td>
<td>19 / 21</td>
</tr>
<tr>
<td>Mean age at onset of dystonia</td>
<td>&lt; 50 yrs.</td>
</tr>
</tbody>
</table>

Dystonia types
- foot dystonia 9
- cranial dystonia 7
- writer’s cramp 6
- cervical dystonia 5
- hemidystonia 3

* LeWitt et al, 1986; Klawans and Paleologos, 1986; Poewe et al, 1988
DYSTONIA IN UNTREATED PD
- L-Dopa effect -
(N = 22 from 3 series*)

Effect on dystonia
improvement 2
worsening 9
equivocal / nil 11

Effect on parkinsonism
improvement 22

* LeWitt et al, 1986; Klawans and Paleologos, 1986; Poewe et al, 1988
Typical manifestations of bradykinesia in PD

- Hypomimia
- Hypophonia
- Micrographia
- Small stepped gait
- Reduced arm swing
- Difficulties rising from a chair or turning in bed
Clinical pharmacokinetics of levodopa

- Levodopa/DDCI has poor bioavailability and short plasma half-life (60–90 min)

- Erratic gastric retention and/or absorption can lead to delays in oral levodopa uptake

- Competition with neutral amino acids (proteins) for transport across gastrointestinal tract and blood-brain barrier

(modified from Nutt and Fellman, 1984)
### Atypical Features in 100 Cases of Postmortem-Confirmed PD

<table>
<thead>
<tr>
<th>Feature</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall frequency</td>
<td>12 patients</td>
</tr>
<tr>
<td>Severe early dementia</td>
<td>5</td>
</tr>
<tr>
<td>No response to adequate levodopa</td>
<td>4</td>
</tr>
<tr>
<td>Early fluctuating confusional states</td>
<td>4</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>2</td>
</tr>
<tr>
<td>Apraxia</td>
<td>2</td>
</tr>
<tr>
<td>Focal dystonia</td>
<td>2</td>
</tr>
<tr>
<td>Early marked dysautonomia</td>
<td>2</td>
</tr>
</tbody>
</table>

Coexistent pathology: cortical Lewy bodies (5); striatal infarcts (2); senile plaques/neurofibrillary tangles (1); none (4)

FREQUENCY OF MUTATIONS IN EARLY-ONSET PD
(Alcalay et al, Arch Neurol 2010)

- N = 953 with clinically defined PD and onset younger than 51 yrs.

- Assessment for mutations in SNCA, PRKN, PINK1, DJ 1, LRRK2, GBA

- 16.6 % positive for mutations (6.7% PRKN, 3.6% LRRK2, 6.7% GBA, 0.2% DJ 1)

- 40.6 % with onset ≤ 30 yrs
# CLINICAL DIFFERENCES BETWEEN PARKIN+ and PARKIN- EOPD


<table>
<thead>
<tr>
<th></th>
<th>PARKIN+</th>
<th>PARKIN-</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease onset</td>
<td>32 a</td>
<td>42 a</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Disease duration</td>
<td>17 a</td>
<td>13 a</td>
<td>0.002</td>
</tr>
<tr>
<td>Dystonia (presenting symptom)</td>
<td>42 %</td>
<td>22 %</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>44 %</td>
<td>21 %</td>
<td>0.04</td>
</tr>
<tr>
<td>LID (after 5 yrs.)</td>
<td>77 %</td>
<td>63 %</td>
<td>0.04</td>
</tr>
<tr>
<td>Slow progression</td>
<td>88 %</td>
<td>72 %</td>
<td></td>
</tr>
</tbody>
</table>
Case:
Male, 36 y, complaining of occasional tremor and unusual leg movements

- Occasional tremor, while drinking, onset at 27 y
- “walking” problems, at 32 y
- Diagnosis of conversion
- Other cases of tremor or PD in the family
- N. Exam: Brisk reflex, slight rigidity.
A multidisciplinary study of patients with early-onset PD with and without parkin mutations (Lohmann et al, Neurology 2009)

- 44 pts with young-onset PD (< 45 yrs)

<table>
<thead>
<tr>
<th></th>
<th>PRKN+</th>
<th>PRKN-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose of LD</td>
<td>528 mg</td>
<td>778 mg</td>
</tr>
<tr>
<td>Duration of tx</td>
<td>13.2 yrs</td>
<td>9.9 yrs</td>
</tr>
<tr>
<td>Prevalence of dyskinesias</td>
<td>71.4 %</td>
<td>61 %</td>
</tr>
<tr>
<td>Time to dyskinesia</td>
<td>12 yrs</td>
<td>10 yrs</td>
</tr>
<tr>
<td>Prevalence of fluctuations</td>
<td>57 %</td>
<td>96 %</td>
</tr>
<tr>
<td>Time to fluctuations</td>
<td>14 yrs</td>
<td>5 yrs</td>
</tr>
</tbody>
</table>
DOES DEFICIENT NIGROSTRIATAL DOPAMINERGIC TRANSMISSION CAUSE DYSTONIA?

- Symptomatic hemidystonia following putaminal lesions (i.e. stroke)
- Acute dystonic reaction following DA-blocking agents
- Dopa-responsive dystonia
<table>
<thead>
<tr>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;D-I-D&quot;-response</td>
<td>Muenter et al, 1977</td>
</tr>
<tr>
<td>&quot;OFF-period dystonia&quot;</td>
<td>Lees et al, 1977</td>
</tr>
<tr>
<td>&quot;Early morning dystonia&quot;</td>
<td>Melamed, 1979</td>
</tr>
<tr>
<td>&quot;Dystonic foot response&quot;</td>
<td>Nausieda et al, 1980</td>
</tr>
<tr>
<td>&quot;Painful dystonic spasms&quot;</td>
<td>Ilson et al, 1984</td>
</tr>
</tbody>
</table>
## Prevalence of LD-Induced Dystonia in PD

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Total Dystonia</th>
<th>Off-Period Dystonia</th>
<th>Peak-Dose Dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schrag et al, 2000</td>
<td>87</td>
<td>?</td>
<td>10 %</td>
<td>?</td>
</tr>
<tr>
<td>Kidron and Melamed, 1987</td>
<td>207</td>
<td>28 %</td>
<td>25 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Wickremaratcbi et al, 2011</td>
<td>358</td>
<td>20 %</td>
<td>13 %</td>
<td>4 %</td>
</tr>
</tbody>
</table>
Dystonia in Parkinson's Disease: Clinical and Pharmacological Features

W. H. Poewe, MD,* A. J. Lees, MD,† and G. M. Stern, MD†
Ann Neurol 1988;23:73-78

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td>Age at PD onset</td>
<td>48.7  (24 - 71) yrs.</td>
</tr>
<tr>
<td>PD duration</td>
<td>9.7   (2 - 20) yrs.</td>
</tr>
<tr>
<td>L-Dopa</td>
<td></td>
</tr>
<tr>
<td>- duration</td>
<td>8.9   (0.25 - 17) yrs.</td>
</tr>
<tr>
<td>- dose/d</td>
<td>654   (300 - 2.000) mg</td>
</tr>
</tbody>
</table>
L-DOPA-INDUCED DYSTONIA IN P.D.

(N = 56; Poewe et al, 1988)

- Relation to L-Dopa response cycle -

* OFF-Period N = 46
* Biphasic N = 7
* Peak-dose N = 9
ETIOPATHOGENESIS OF PD
- Hypotheses -

• Environmental factors
  - toxic
  - infectious
  - unknown

• Genetic factors
  - causative genes (LRRK2, SNCA, VPS35, PRKN, DJ1, PINK1)
  - risk genes (GBA)

• Age
Significantly higher DAT binding in L vs. R striatum
\((V_3 \, ^{2\, \prime\prime} \, L \, vs. \, R \, p<0.0001)\)

van Dyck et al, 2002
Handedness Correlates with the Dominant Parkinson Side: A Systematic Review and Meta-analysis

Anouk van der Hoom, BSc,1* Huibert Burger, MD, PhD,2,3 Klaus L. Leenders, MD, PhD,1 and Bauke M. de Jong, MD, PhD1

1Department of Neurology, University Medical Center Groningen, University of Groningen, The Netherlands
2Interdisciplinary Center for Psychiatric Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands
3Department of Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands

Mov Disord 2012;27:206-10

<table>
<thead>
<tr>
<th>Study</th>
<th>R-handed</th>
<th>L-handed</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akerman (2008)</td>
<td>PD.R = 78</td>
<td>PD.L = 70</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Barrett (2010)</td>
<td>PD.R = 524</td>
<td>PD.L = 403</td>
<td>37</td>
<td>51</td>
</tr>
<tr>
<td>Reynolds (1971)</td>
<td>PD.R = 43</td>
<td>PD.L = 36</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Sawar (2010)</td>
<td>PD.R = 154</td>
<td>PD.L = 69</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Stewart (2009)</td>
<td>PD.R = 238</td>
<td>PD.L = 153</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Štochil (2009)</td>
<td>PD.R = 218</td>
<td>PD.L = 168</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Van der Hoom (2011)</td>
<td>PD.R = 158</td>
<td>PD.L = 96</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>Van Roden (2009)</td>
<td>PD.R = 129</td>
<td>PD.L = 104</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Yust-Katz (2008)</td>
<td>PD.R = 132</td>
<td>PD.L = 106</td>
<td>9</td>
<td>13</td>
</tr>
</tbody>
</table>

Total (95% CI)        | 2413      | 1644     | 142    | 206                          | 2.13 [1.71-2.66] |

Percentage %          | 59.5      | 40.5     | 40.8   | 59.2                         |

Heterogeneity: Chi² = 14.06, df = 9 (p = 0.12); I² = 36%
Test for overall effect: Z = 6.66 (p < 0.0001)
Handedness and motor symptom asymmetry in Parkinson’s disease
- Barrett et al, J NNP 2011 -

<table>
<thead>
<tr>
<th>Pts. with asymm. onset (N=1015)</th>
<th>Side of onset</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dominant (N=575)</td>
<td>Non-dominant (N=440)</td>
</tr>
<tr>
<td>Initial motor symptom, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>380 (66.1)</td>
<td>292 (66.4)</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>101 (17.6)</td>
<td>40 (9.1)</td>
</tr>
<tr>
<td>Rigidity</td>
<td>53 (9.2)</td>
<td>54 (12.3)</td>
</tr>
<tr>
<td>Gait difficulty</td>
<td>23 (4.0)</td>
<td>40 (9.1)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (3.1)</td>
<td>14 (3.2)</td>
</tr>
</tbody>
</table>
Template-based ROI-Analysis

original image  spatially normalised

spatial normalisation

template image  deformation field

Ashburner et al., Hum Brain Mapp 2001
Template-based ROI-Analysis

Ashburner et al., Hum Brain Mapp 2001
Correlations of nigral and olfactory MRI diffusivity and striatal Dopa PET uptake in Parkinson’s disease - demographic data

<table>
<thead>
<tr>
<th></th>
<th>Parkinson’s disease n = 16</th>
<th>Controls n = 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male (n)</td>
<td>10/6</td>
<td>8/6</td>
</tr>
<tr>
<td>Age at scan (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>68.1 ± 6.1 (54.8–76.3)</td>
<td>67.3 ± 3.7 (60–74.4)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.7 ± 3.7 (0.1–15.2)</td>
<td></td>
</tr>
<tr>
<td>UPDRS motor score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>20 ± 10.3 (8–42)</td>
<td></td>
</tr>
<tr>
<td>Hoehn and Yahr staging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.3 ± 1 (1–4)</td>
<td></td>
</tr>
<tr>
<td>Total odour score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>19.2 ± 4.4 (12.3–28.5)**</td>
<td>34.3 ± 2.2 (31.3–37.3)***</td>
</tr>
<tr>
<td>Odour threshold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.8 ± 2.6 (1–9.8)**</td>
<td>7.3 ± 2.2 (4.3–12)</td>
</tr>
<tr>
<td>Odour discrimination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>8 ± 1.9 (5–13)**</td>
<td>13 ± 1.4 (10–15)***</td>
</tr>
<tr>
<td>Odour identification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7.4 ± 2.9 (3–13)**</td>
<td>13.9 ± 0.9 (12–15) ***</td>
</tr>
</tbody>
</table>
Correlations of nigral and olfactory MRI diffusivity and striatal Dopa PET uptake in Parkinson’s disease

Scherfler et al., Brain 2013
Correlations of nigral and olfactory MRI diffusivity and the UPDRS motor score in Parkinson’s disease.

\[ r = -0.48, P < 0.01 \]

\[ r = 0.59, P < 0.01 \]
PARKINSON’S DISEASE
- Differential clinical symptoms -
  (Hughes et al, 1992)

- Asymmetric onset
- Presence of classical rest tremor
- Absence of atypical features
- No evidence for alternative pathogenesis
REST TREMOR IN PD
Decades of Delayed Diagnosis in 4 Levodopa-Responsive Young-Onset Monogenetic Parkinsonism Patients

Helen Ling, BScMed, BMBS, MSc,1,2 Mark Braschinsky MD, PhD,3 Pille Taba, MD,3 Siiri-Merike Lüüs, MD,3 Karen Doherty, MB, BCh, BAO, MRCP,1,2 Anna Hotter, MD,4 Werner Poewe, MD,4 and Andrew J. Lees, MD FRCP1,2*

Movement Disorders, Vol. 26, No. 7, 2011
• 43 year old male

• Involuntary cramping L foot for 9 mths.

• Occur exclusively following > 15 minutes of walking

• Painful

• Immediate cessation with rest

• Neurological findings outside of attacks normal
Abstract—Isolated foot dystonia following exercise is a rare manifestation of early PD. It may precede the onset of parkinsonism by years and can be clinically indistinguishable from familial exercise-induced dystonia. The authors present a patient with dystonic claudication where dopamine transporter SPECT using $^{123}$I-FP-CIT allowed early diagnosis of PD and enabled effective symptomatic treatment with a dopamine agonist.

PARALYSIS AGITANS;
WITH AN ACCOUNT OF A NEW SYMPTOM.
BY PURVES STEWART, M.A., M.D. EDIN.,
M.R.C.P. LOND.,
SENIOR HOUSE PHYSICIAN TO THE NATIONAL HOSPITAL (FOR THE
PARALYSED AND EPILEPTIC, QUEEN-SQUARE, BLOOMSBURY,
LONDON, W.C.)
DYSTONIA IN PARKINSON’S DISEASE

„The patient complains, when walking, that the toes of one foot occasionally become spontaneously strongly flexed and curled up under the sole in a cramp-like fashion, causing difficulty in walking. This „curling up“ of the toes is often so uncomfortable that the patient has to stand still for a minute or two until he can get his toes to relax and spread out flat again. All the toes, with the exception of the great toe, participate in this flexor contracture (...). In some cases the contraction may spread to the anterior tibial muscles, causing an inversion of the ankle as well.“

Purves-Stewart, 1898
## Dystonia as a Presenting Symptom in Early Onset PD (EOPD)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>Dystonia at Onset</th>
<th>Pts. with Autosomal-Recessive PD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schrag et al, 1998</td>
<td>139</td>
<td>14 %</td>
<td>nd</td>
</tr>
<tr>
<td>Lücking et al, 2000</td>
<td>186</td>
<td>22-42 %</td>
<td>54 % *</td>
</tr>
<tr>
<td>Chung et al, 2006</td>
<td>94</td>
<td>6 %</td>
<td>5 % *</td>
</tr>
<tr>
<td>Lohmann et al, 2009</td>
<td>44</td>
<td>52 %</td>
<td>50 % *</td>
</tr>
<tr>
<td>Wickremaratchi et al, 2011</td>
<td>70</td>
<td>20 %</td>
<td>29 % <em>/</em>*</td>
</tr>
</tbody>
</table>

* Parkin; ** PINK-1
DYSTONIA IN PD
- Classification -

1. Focal Dystonia as a presenting symptom
   - Sporadic PD
   - Autosomal-recessive PD
     (Parkin, DJ-1, PINK1)

2. Drug-induced dystonia
   - L-Dopa
   - DA-agonists

3. Postural abnormalities in PD
   - Deformities of the hands and feet
   - Abnormal axial postures
     * „Antecollis“
     * Camptocormia
     * Lateroflexion (Pisa-Syndrome)