Parkinson’s disease: Disease progression and mortality

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Professor Richard Walker
Consultant Physician and Honorary Professor of Ageing and International Health
Northumbria Healthcare NHS Foundation Trust
Institute of Health and Society, Newcastle University
Talk content

- Motor systems
- Non-motor systems
- Pain
- Prevalence of palliative care symptoms
- Where do patients die?
- What do they die from?
During the presymptomatic phase of Parkinson's disease there is gradual loss of dopaminergic neurons in the substantia nigra until a critical threshold is reached, at which time motor symptoms first appear. The motor symptoms then progress and become associated with other signs of Parkinson's disease.
The ‘Braak hypothesis’

Stage 1 and 2:
Pathology confined to certain structures in the brain stem, not yet the substantia nigra

Stage 3 and 4:
Pathology spreads to the midbrain and basal ganglia

Stage 5 and 6:
Changes spread to the cortex

Image adapted from The Professionals Guide to Parkinson’s Disease, Parkinson’sS
The ascending pathological process in PD
Late stage disease

- Moderate disability + independent.
- Dependency is unavoidable. Spouse is the carer.
- Increasing physical deficits.
- Communication problems.
- Cognitive problems.
- Less responsive to drugs / increasing complications.
Specific problems in PD

- Motor complications
- Falls
- Sleep problems
- Autonomic dysfunction
- Neuropsychiatric problems
Typical pattern of wearing-off during the day

Adapted from EPDA: Taking Control. Parkinson's leaflet information series
Neuropsychiatric symptoms:
- Dementia
- Depression
- Apathy
- Anxiety
- Loss of libido

Autonomic symptoms:
- Constipation
- Urinary incontinence
- Erectile dysfunction
- Excessive sweating
- Postural hypotension
- Excessive salivation

Sleep disturbance:
- REM sleep disorder
- RLS
- Vivid dreams
- Daytime somnolence
- Dystonia

Sensory symptoms:
- Pain
- Paraesthesia
Sleep Disorders

- Two thirds of patients
- Insomnia
  - Initial
  - Sleep maintenance (sleep fragmentation)

Parasomnias
- REM sleep behaviour disorder
- Vivid dreams

- Excessive daytime sleepiness and sleep attacks
- Obstructive sleep apnoea and stridor (NB MSA)
Autonomic disturbances

- Constipation
- Urinary incontinence
- Impotence
- Orthostatic hypotension
- Sweating
- Pain
- Dysphagia
- Seborrhoea / Blepharitis
NEUROPSYCHIATRIC COMPLICATIONS
Depression, Anxiety and Apathy Associated with Parkinson's

Depression
• The prevalence is estimated at between 30 and 40%

Anxiety
• Generalised anxiety, agitation, panic attacks and phobic disorders can occur in up to 40% of people with PD

Apathy
• More likely to be a direct consequence of disease related physiological changes than a psychological reaction or adaptation to disability

In Parkinson’s patients with depression there is a higher frequency of

Dysphoria
Sadness
Irritability
Pessimism about the future
- Depression
- Anxiety and agitation
- Sleep disturbances
- Vivid dreams
- Hallucinations
- Delirium
- Dementia
Cholinesterase Inhibitors

- Rivastigmine license for PD dementia (March 2006)
- Improvement in cognition, behaviour and hallucinations
- Appear to be more effective in PD dementia and Lewy Body dementia than in AD and vascular dementia
- Relative cholinergic excess in PD
- Donepezil now off patent
Typical case

- Man aged 78 - PD for 16 years with recent cognitive decline
- Recurrent admissions – falls, chest infections, urinary tract infections with associated hallucinations and increased confusion
- Now admitted unable to swallow – NG tube
- Discussions with family about artificial feeding (PEG tube) and where patient should be cared for
- What would the patient have wanted?
Natural history in IPD

I : unilateral disease with minimal functional impairment (1-3 years)
II : bilateral or midline involvement without balance impairment (6 years)
III : Postural instability- some restriction in activity but independent (7 years)
IV : severely disabled disease; patient is markedly incapacitated (9 years)
V : restricted to bed or wheelchair (14 years)
Described a four stage model of PD

- Diagnosis (1.6 years +/- 1.5)
- Maintenance (5.9 years +/- 4.8)
- Complex (4.9 years +/- 4.4)
- Palliative (2.2 years +/- 2.2)
Palliative care

Palliative care is defined as:

“an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.” (WHO 2002)
Time course of the disease
- MacMahon et al 2004/05
Categories of pain

- Musculoskeletal
- Radicular or neuropathic
- Dystonic
- Akathitic discomfort
- Primary, or central, Parkinsonian pain
Area
Demographics

- N = 123
- Male = 59
- Age: median = 75.4 (range 51-89)
- H+Y stage: median = 3.0 (range 1-5)
- MMSE: median = 28 (range 19-30)
Pain in PD

- Overall pain in PD is present in 85%
- PD pains were found in 62.6%
- Non PD pains were found in 64.2%
- Most PD pain is intermittent
- Non PD pain is generally more severe
- Pain does not get worse with disease progression
- Analgesic use suggests that pain is under treated

Symptoms
# Most common symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slowness of movement</td>
<td>109</td>
<td>88.6%</td>
</tr>
<tr>
<td>Pain</td>
<td>104</td>
<td>85%</td>
</tr>
<tr>
<td>Tremor</td>
<td>91</td>
<td>74%</td>
</tr>
<tr>
<td>Drooling</td>
<td>80</td>
<td>65%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>76</td>
<td>61.8%</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>75</td>
<td>61%</td>
</tr>
<tr>
<td>Stiffness</td>
<td>75</td>
<td>61%</td>
</tr>
<tr>
<td>Immobility</td>
<td>72</td>
<td>58.5%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>66</td>
<td>53.7%</td>
</tr>
<tr>
<td>Memory problems</td>
<td>63</td>
<td>51.2%</td>
</tr>
</tbody>
</table>
### ‘Palliative care type’ symptoms

<table>
<thead>
<tr>
<th>Symptoms (Cancer)</th>
<th>Ellershaw et al</th>
<th>Frequency Ellershaw et al (n = 125)</th>
<th>Frequency Current study (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
<td>74%</td>
<td>85%</td>
</tr>
<tr>
<td>Immobility</td>
<td></td>
<td>66%</td>
<td>58.5%</td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>~50%</td>
<td>13%</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td>~40%</td>
<td>49.6%</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>~30%</td>
<td>23.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>~26%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Dyspnoea/ SOBOE</td>
<td></td>
<td>~20%</td>
<td>35.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>~15%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

Lee MA et al Parkinsonism and Related Disorders 2007
Pain prevalence studies

- 15 studies (5 with controls) report prevalence between 25% and 85%
- Variable definitions of pain, e.g., acute versus chronic
- Several classifications for nociceptive and neuropathic pain
Treatment considerations

- Physiotherapy – early, prevention
- If fluctuations consider adjusting dopaminergic medication
- Simple analgesics
- Opioids – constipation already a problem in PD, can cause night terrors
- Meditation
Pain key messages

- Pain is common in PD
- May not be volunteered by patient
- Important to identify cause of pain to guide treatment
- May be directly related to PD but usually not
- If related to wearing off adjustment of PD treatment may help
Other problems

- Swallowing issues
- Breathlessness – aspiration pneumonia
- Communication issues
  - Cognitive impairment
  - Speech problems
  - Advanced care planning
- Complex symptoms
- Reducing therapeutic options
How do we identify those who are dying?
The presence of 2 or more of the criteria should trigger inclusion on the PC register

- Drug treatment is no longer effective/ an increasingly complex range of drug treatments
- Reduced independence, need for help with daily living
- Recognition that the disease has become less controlled with less predictable “off” periods
- Dyskinesias, mobility problems and falls
- Swallowing problems
- Psychiatric signs (depression, anxiety, hallucinations, psychosis)
Prognosis in IPD


- Related to respiratory infections

- Life expectancy [Ishihara JNNP 2007]
  - 25-39 years at onset = 38yrs vs 49yrs (control)
  - 40-64 years at onset = 21yrs vs 31yrs
  - >65 years at onset = 5yrs vs 9yrs

- Prognostic factors for progression [Post B et al Mov Dis 2007]
  - Higher age of onset
  - Higher postural instability and gait disorder
Predictors of mortality

- Based on falls cohort recruited at NTGH in 2000
- Abnormal autonomic function tests do not predict mortality\(^1\)
- The results of physiotherapy assessment including mobility and balance do predict mortality\(^2\)

Where, and of what, do patients die?
Trends in place of death (UK)

- Cancer deaths at home – falling
  - (1974 – 31.2%; 2003 – 22.1%)

- Non cancer deaths at home, - falling
  - (1974 – 31%; 2003 – 16.7%)

- Future predictions – by 2030 <10% die at home

- Implications for service provision
Methods

- Data requested from the Office of National Statistics (ONS)
  - place of death and cause of death (obtained from death certification)
- ONS provided details of data entered on death certificates and the Underlying cause of death as produced by the coding system
- Data provided prior to 2001 was classified using ICD 9, subsequent data is classified using ICD 10
- 227 patients registered on the North Tyneside Parkinson’s Disease Database
  - 143 - Idiopathic Parkinson’s Disease (IPD)

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## Cause of Death Compared to Literature

<table>
<thead>
<tr>
<th>Authors</th>
<th>IHD PD</th>
<th>IHD Control</th>
<th>Cerebrovascular PD</th>
<th>Cerebrovascular Control</th>
<th>Malignancy PD</th>
<th>Malignancy Control</th>
<th>Pneumonia PD</th>
<th>Pneumonia Control</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Schlomo et al</td>
<td>23%</td>
<td>26%</td>
<td>17%</td>
<td>14%</td>
<td>4.6%</td>
<td>16.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall et al</td>
<td>13%</td>
<td>27.5%</td>
<td>6%</td>
<td>16%</td>
<td>8%</td>
<td>19%</td>
<td>23%</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>D’Amelio et al</td>
<td>27%</td>
<td>35%</td>
<td>20%</td>
<td>22%</td>
<td>7%</td>
<td>7%</td>
<td>27%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Beyer et al</td>
<td>13%</td>
<td>21%</td>
<td>9%</td>
<td>10%</td>
<td>17%</td>
<td>25%</td>
<td>20%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>North Tyneside population (IPD)</td>
<td>12%</td>
<td>-</td>
<td>9%</td>
<td>-</td>
<td>12%</td>
<td>-</td>
<td>11%</td>
<td>-</td>
<td>29%</td>
</tr>
</tbody>
</table>
1a on the Death Certificate was pneumonia in 45%

Nath et al – commonest cause of death in patients with PSP was pneumonia, occurring in 45% of patients
Death certification

<table>
<thead>
<tr>
<th>PD mentioned on Death certificate</th>
<th>89 (63%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD NOT mentioned on Death certificate</td>
<td>53 (37%)</td>
</tr>
</tbody>
</table>

Other Research

- Beyer et al (2001) – PD mentioned in 50-60% of pts
- Nath et al (2005) – PSP mentioned in 65% of patients with known PSP
## Place of Death

<table>
<thead>
<tr>
<th></th>
<th>General Population (age &gt;60yrs)</th>
<th>IPD - Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOME</strong> (p&lt;0.05)</td>
<td>16.5%</td>
<td>12 (8.4%)</td>
</tr>
<tr>
<td><strong>CARE HOME</strong></td>
<td>20.6%</td>
<td>52 (36.4%)</td>
</tr>
<tr>
<td>(including continuing care)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HOSPITAL</strong></td>
<td>58.7%</td>
<td>79 (55.2%)</td>
</tr>
<tr>
<td><strong>HOSPICE</strong></td>
<td>2.7%</td>
<td>0</td>
</tr>
</tbody>
</table>

Survival - Africa

- Longitudinal study (Nigeria) of the predictors of mortality in patients with PD
- 28 cases of PD and age and sex-matched controls followed for 6 years
- Patients with PD were more likely to die (case fatality rate of 25% compared with 7% in controls)
- Older patients, older age at onset and more severe disease (H & Y) had higher mortality rates

Hai 3 year follow up

- Only one stopped medication due to side effects (dyskinesia)
- At 3 years, 9/16 experienced wearing off and a further three had dyskinesias
- Non motor symptoms were a problem at initial assessment and continued to be a problem for many of the patients
- Wearing off 11/16
- 15/33 patients from the prevalence study in 2005 had died by 2010

Dotchin et al J Neurol 2011; 258(9):1649-56
Typical case

- Man aged 78 - PD for 16 years with recent cognitive decline
- Recurrent admissions – falls, chest infections, urinary tract infections with associated hallucinations and increased confusion
- Now admitted unable to swallow – NG tube
- Discussions with family about artificial feeding (PEG tube) and where patient should be cared for
- What would the patient have wanted?
Key Learning Points

- PD does affect life expectancy, particularly in sub-Saharan Africa where there is limited access to diagnosis and drug treatment.
- Complex motor symptoms – wearing off, dyskinesia.
- Non-motor symptoms have a major impact, especially cognitive impairment.
Thank you
Musculoskeletal

- Pain in joints and muscles
- Associated findings – skeletal deformity, limited joint mobility, postural abnormalities
- Exacerbated by Parkinsonian rigidity and immobility, and relieved by mobility
- May improve with levodopa
- Frozen shouler may be a presenting symptom
- Spinal deformities can become very marked – camptocormia
- Exercise programme, NSAIDs, passive exercises to prevent contractures
Radicular/neuropathic

- Pain in a root or nerve territory
- Associated with motor or sensory signs of nerve or root entrapment
- Therapy and potentially surgery
Central/primary pain

- Burning, tingling sensations not confined to root or nerve territory
- May have autonomic character, with visceral sensations (abdominal bloating) or dyspnoea (chest wall tightening)
- May vary with medication cycle but not explained by dystonia or musculoskeletal pain
- Unusual pain syndromes involving face, head, pharynx, epigastrium, abdomen, pelvis, rectum and genitalia
- Peripheral nerve blockade does not abolish pain
- Dopaminergic medication may help. Also consider neuropathic pain agents, e.g., Amitriptyline, Gabapentin, Pregabalin.
Dystonia

- Associated with sustained twisting movements and postures
- Typically foot but may involve any limb or extremity, as well as facial and pharyngeal musculature
- Fluctuates with medication dosing, usually when “off” (NB can get peak dose dystonia)
- Adjustment of PD medication
Akathisia

- Subjective sense of restlessness with urge to move
- May fluctuate with medication effect
- Improves with l’dopa
- May be due to dopaminergic deficiency in the mesocortical pathway originating in the ventral tegmental area
- Also occurs in postencephalitic Parkinsonism and neuroleptic-induced akathisia
PD specific pains

- Coat-hanger
- Oro-facial
- Burning mouth syndrome