Motor Fluctuations in Parkinson’s Disease

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Outline

• Type of fluctuations
• Motor fluctuations, end of dose, dyskinesia.
• Complicated fluctuations
• ?Causes

(Commonly under diagnosed)
Three Factors

- Stages of Disease
- Change in Environment
- Drug Therapy
Variation Due to Underlying Disease

• Stiffness, slowness and freezing
  – Problem with control of posture position
  – Start hesitation (also in other ADL)

• Paradoxic Kinesis
  – With emotion, stress or fear
  – (Not self well)
Variation Due to Underlying Disease (cont’d)

• Emotion and awareness
  – Stress, tremor, > rigidity
  – Rigidity & contralateral activation

• Sleep and sleep benefit (~20% of PD)
  – In treated and untreated patients
Variation Due to Underlying Disease (Cont’d)

Fatigue and Neurasthenia:

– Can’t keep up strength, writing, voice etc

– Especially programmed 2 movements or more
Variation Due to Treatment

• Medium Duration Response
  – Short duration improvement of Muehler (1971)
  – 3 to 5 hours (related to LDOPA level)

• Long Duration Response
  – ? Storage phenomenon
Levodopa: Short-term problems

- Poor bioavailability and short plasma half-life
- Erratic gastric retention and/or intestinal absorption-delays oral levodopa uptake
- Competition with neutral amino acids (proteins) for transport across gastrointestinal tract and blood–brain barrier
Variation Due to Treatment

- “Swings” - from on (all) to off (none)
- Dose related or unrelated
- Predictable or unpredictable
  - Related to fatigue or food
Typical pattern of wearing-off

Daily fluctuations in wearing-off

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Useful definitions of wearing-off

For the physician:

“Wearing-off refers to the predictable emergence of one or more PD signs or symptoms before the next scheduled antiparkinsonian medication dosage.”

Stacy et al, 2004

For the patient:

“Wearing-off happens when a dose that previously used to help your symptoms does not last as long and your next dose is needed sooner. Symptoms of wearing-off include changes in movement and mobility, thoughts and feelings, sensations and sense of well being.”

PinK working group

“A generally predictable recurrence of motor or non motor symptoms that precedes a scheduled dose and usually improves with antiparkinsonian medication.”

2004 PD working group

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End of Dose Deterioration
“Wearing Off”

?? Cause

- Disease progression and LDOPA level
  (Not pharmacokinetic)
- Change in dietary a.a.
- No tolerance (except emetics)
Within two years 12% of neurologists recognize wearing-off but 54% modify the levodopa regimen. The large discrepancy in the numbers (54% Vs 12%) highlights the difficulty in identifying the first signs of wearing-off.

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Long-term problems:
Symptoms unresponsive to levodopa
Parkinson's Disease Symptoms

**Motor**
- Recurring Parkinsonism
- Dystonia

**Psychiatric**
- Panic
- Depression
- Paranoia, hallucinations

**Sensory**
- Paresthesias
- Pain

**Autonomic**
- Tachycardia
- Sweating
- Constipation
- Belching
- Shortness of breath
Long-term (Intermediate) problems

Wearing-off

~ 40% of patients affected within 2 years

- The early symptoms of wearing-off can be subtle and difficult to identify as associated with PD treatment
- Wearing-off symptoms can also be non-motor, and can include: anxiety, fatigue, mood lowering, restlessness and autonomic dysfunction
- Early recognition and treatment or prevention of wearing-off would allow better and more consistent long-term symptom control

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Fahn et al. 2002
Witjas et al. 2002
Rascol et al. 2000
Schrag et al. 2000
Complicated End-of-Dose Effect

Predictor

- Large amplitude finger movements
- LDOPA test dose
- On-Off Chart
## Prevalence of levodopa-associated motor complications

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Prevalence of complication</th>
<th>Length of study (years)</th>
<th>Method of evaluation</th>
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</thead>
<tbody>
<tr>
<td>Poewe et al. 1986</td>
<td>52% wearing off</td>
<td>6</td>
<td>Webster scale</td>
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<tr>
<td></td>
<td>54% dyskinesias</td>
<td></td>
<td>Modified Columbia Scale</td>
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<td>Hely et al. 1994</td>
<td>41% wearing off</td>
<td>5</td>
<td>Modified Columbia Scale</td>
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<td>physician evaluation</td>
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<tr>
<td>Montastruc et al. 1994</td>
<td>34% wearing off</td>
<td>5</td>
<td>Columbia Scale, UPDRS</td>
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<td>48% dyskinesias</td>
<td></td>
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<tr>
<td>Dupont et al. 1996</td>
<td>59% fluctuations</td>
<td>5</td>
<td>UPDRS, part IV</td>
</tr>
<tr>
<td>DATATOP. 1996</td>
<td>50% wearing off</td>
<td>2</td>
<td>Physician evaluation</td>
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<tr>
<td></td>
<td>30% dyskinesias</td>
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<td>UPDRS, part IV</td>
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<tr>
<td>Rascol et al. 2000</td>
<td>45% dyskinesias</td>
<td>5</td>
<td>UPDRS, dyskinesia scale</td>
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<tr>
<td>PSG. 2000</td>
<td>30% dyskinesias</td>
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<td>Physician evaluation</td>
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<td>Rajput et al. 2002</td>
<td>15% dyskinesias</td>
<td>2.6</td>
<td>Physician evaluation</td>
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<tr>
<td></td>
<td>31% dyskinesias</td>
<td>6.4</td>
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</tbody>
</table>
Peak Dose Dyskinesia: Changes in levodopa response

**Early disease**
- Smooth, long duration of clinical benefit
- Low incidence of dyskinesias

**Mid-stage disease**
- Diminished duration of clinical benefit
- Increased incidence of dyskinesias

**Advanced disease**
- Clinical response mirrors levodopa plasma pharmacokinetic profile
- ‘On’ time is associated with dyskinesias
In PD, pulsatile delivery of traditional levodopa leads to pulsatile stimulation of dopamine receptors.
In PD, pulsatile stimulation causes further changes in gene expression in the already unstable basal ganglia

Pre-proenkephalin B (marker for dyskinesia) mRNA expression in the caudate-putamen

Non-parkinsonian patient

PD patient with dyskinesia
Pulsatile stimulation leads to gene changes in the basal ganglia of MPTP primates whereas continuous stimulation does not.

Preproenkephalin-B (marker for dyskinesia) mRNA expression in the striatum.
Diphasic Dyskinesia

- Younger patient (in 5 – 10%)
- Legs in affected side
  - Rhythmic, chronic or ballistic movements (vs. sz.)
  - Dystonia (20%) Painful associated with autonomic S/S
- Second phase is longer
- May improve by increasing Ldopa!
Early Morning Dystonia

• Unilateral (most affected side)
• Painful after 2 – 6 years of LDOPA Rx
• Related to chronic low level of LDOPA
Random Oscillations “Yo-Yo”

- No-on
- Delayed-on
- 10 – 15% of advanced PD
Random Oscillations
(“on-off” phenomenon)

• In evenings, no help with Rx changes
• No on or delayed on
• May lead to LDOPA dependence
• Receptor refractory events
• Seen with falling phase of LDOPA level

Cause:
  – ?? Competitive blockage by metabolites
  – ?? Related to sudden desensitization block of dopamine
Deep Brain Stimulation
(DBS – STN)
Duodopa Therapy
Levodopa: Long-term problems

• Some PD symptoms respond poorly or not at all to levodopa (Possible neurotoxicity?)

• Changes in levodopa response and the development of complications:
  
  – motor fluctuations (wearing-off, ‘on–off’ fluctuations)
  – dyskinesia (peak dose, diphasic, ‘off’-period dystonia)
  – mental status changes (confusion, hallucinations, psychosis)
Conclusion

Underdiagnosed, Treatable, Fluctuates, Disabling
برنامج الاضطرابات الحركية

كتيب عن برنامج الاضطرابات الحركية

在他的 موقع: إن اصدار المواقع الإلكترونية لبرنامج الاضطرابات الحركية جاء ليوفر التطور في أساليب التواصل مع الجهات المتغيرة بذكاء، مثل الهيئات المحلية والآليات، وأفراد المجتمع. يمكن من خلاله التعرف على هذا البرنامج والاستفادة من تنشيطه المختلفة.

كلمة رئيس المدرسة التنفيذية: سميغ

كلمة رئيس برنامج الاضطرابات الحركية: النظير الكلي
Parkinson Disease in Saudi Arabia
Movement Disorder Program

www.kfshrc.edu.sa/mdp

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– Nael Hasan, Coordinator
Thank you.