Parkinson’s disease

Dr Mark Edwards
Sobell Department of Motor Neuroscience and Movement Disorders, UCL
&
National Hospital for Neurology and Neurosurgery
CONTENTS.

Chap. I.
DEFINITION—HISTORY—ILLUSTRATIVE CASES.............. 1

Chap. II.
PATHOGENOMONIC SYMPTOMS EXAMINED—TREMOR COACTUS—SCLOTERYBE FESTINANS.................... 19

Chap. III.
SHAKING PALSY DISTINGUISHED FROM OTHER DISEASES WITH WHICH IT MAY BE CONFOUNDED..... 27

Chap. IV.
PROXIMATE CAUSE—REMOTE CAUSES—ILLUSTRATIVE CASES............................................. 33

Chap. V.
CONSIDERATIONS RESPECTING THE MEANS OF CURE, 56

---46---

AN ESSAY ON THE
SHAKING PALSY.

CHAPTER I.
DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (Paralysis Agitans.)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

The term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-
A traditional view of Parkinson’s Disease

- A single disease that causes:
  - Rest tremor
  - Slowness of movement
  - Stiffness of muscles
  - Gait disturbance
Parkinson’s Disease is more complex

• There is (probably) more than one Parkinson’s disease
  – Different genetic forms
  – Tremor dominant
  – Akinesia dominant
  – Cognitive dominant
  – Different rates of progression
  – Different rates of drug complications

• There is much more to Parkinson’s disease than motor symptoms
  – Depression
  – Dementia
  – Pain
  – Constipation
  – Urinary Symptoms
  – Sleep Disorders
  – Loss of sense of smell
  – Plus many others...
What is happening in the brain?
Why?

UNDERLYING GENETIC VULNERABILITY

ENVIRONMENTAL MODIFIERS
Making the diagnosis

• “Premotor phase”
  – Depression, sleep disturbance, loss of sense of smell

• Clinical onset
  – Gradual
  – Often noticed by others first
  – Tremor
  – Often “vague” symptoms
What do we look for?

• Rigidity
  – Stiffness of the limb in both flexion and extension

• Bradykinesia
  – More than just slowness

• Tremor
  – Present at rest, and sometimes on posture
Tests?

• Parkinson’s disease remains a clinical diagnosis.
• There are rare “look-a-like” conditions that can be very difficult to tell apart, especially at the beginning.
How to link loss of dopamine to Parkinson’s symptoms

What do I expect?  What did I get?  ERROR

Sensory Feedback

Dopamine
Cueing and paradoxical kinesis – getting access to motor memories
What can we do?

• The basic idea behind current treatment is to replace dopamine stimulation in the brain.

• The holy grail is to find treatment to slow, stop or even reverse the underlying disease.
Tyrosine
Tyrosine Hydroxylase

Dopa Decarboxylase

Dopamine

HVA

MAO

Blocked by SELEGILINE and RASAGILINE

DAT

ROPINIROLE
PRAMIPEXOLE
CABERGOLINE
PERGOLIDE
ROTIOTINE
APOMORPHINE

COMT

HVA

? Blocked by TOLCAPONE

dopamine receptor

BRAIN

PERIPHERY

Blocked by BENESERAZIDE and CARBIDOPA

Dopa Decarboxylase

DOPAMINE

LEVODOPA

COMT

3-O-METHYLDOPA

Blocked by ENTACAPONE and TOLCAPONE
Levodopa – the original and still the best

• A “direct replacement” for lost dopamine

• The clinically most effective drug with the fewest acute side effects.

• BUT...long term issues with dyskinesia and fluctuations
Dyskinesia

Honey moon  Wearing-off  On-off
Hedonistic Homeostatic Dysregulation

Dopamine Dysregulation Syndrome

Hypersexuality

Punding

Drug Abuse

COMPULSIVE SHOPPING
As time goes on, medication becomes more complex
As time goes on, medication becomes more complex.

**Diagram:**
- **ON** and **OFF** periods.
- Time in hours: 6 to 5.
- DYSKINESIA peak.
- Medication: 2 x Sinemet 125mg Ropinirole 5mg at 6, 9, and 12 hours.
- 1 x Sinemet CR at 22 hours.

**Suggested changes to medication:**
- 1.5 x Madopar 125mg Entacapone 200mg Ropinirole 5mg at 18 hours.
- 1 x Sinemet CR if wakes at night.
Non-motor symptoms

• Treatment is difficult, but is available.

• Key problem is that doctors don’t ask and patients don’t tell.

• Non-motor symptoms are probably the most important determinant of quality of life.
Treatment timings – motor symptoms

- Honey moon
- Wearing-off
- On-off

Conventional treatment
- Apomorphine
- DBS
- Duodopa

Neuroprotective treatment
Apomorphine – an injectable dopamine agonist
Ablative surgery

Deep Brain Stimulation
The standard kit
Established targets for the treatment of PD

**Targets**

- Thalamus
- Internal pallidum (GPi)
- Subthalamic Nucleus (STN)

**Symptoms**

- Tremor
- Dyskinesias
- Dystonia
- Most dopasensitive symptoms
Unilateral Left VIM DBS for Right sided resting and postural Tremor
Selection of PD patients for DBS

Selection criteria aim at making sure that the patient is likely to benefit from surgery and that the risks are not too high.

In the ideal world....

- Rather young patient
- Definite diagnosis of Parkinson’s disease
- Duration of disease not too long
- Dopa-sensitive symptoms
- Intact speech intelligibility
- Normal brain MRI
- No co-morbidities
- No cognitive decline
- No previous or ongoing depression
- No previous or ongoing behavioral problems
- Patient support readily available
- Stable and harmonious familial and social situation
- Realistic expectations from surgery
The current state of play

• Patients under 70 with a clear diagnosis of PD.
• Clearly dopa responsive symptoms but with dyskinesia/fluctuations/tremor poorly responsive to medical therapy.
• Little or no cognitive problems, psychiatric problems, co-morbidities, on-period falls/freezing.
Intra-jejunal L-dopa (Duodopa)
The future

- Focus on neuroprotection/disease modification
  - Can we detect people with PD before they manifest symptoms?
  - Should we start treatment earlier?
  - What about non-motor symptoms/non-dopa responsive symptoms?

- Modifying current treatments
  - Drug administration
  - New targets for DBS
  - Earlier DBS?