Bradykinetic disorders

Dr Natanya Fourie
Neurologist
Background information

• Movement disorders divided into 2 main groups

- BRADYKINETIC
  - REDUCED

- HYPERKINETIC
  - EXCESSIVE
Bradykinetic

• Slowed ability to start/continue movement

• Impaired ability to adjust the body’s position

• Rigidity

• Postural instability

• Loss of automatic associated movements
Basal Ganglia

BG ↓ (output)
Thalamus ↓
Cerebral Cortex ↓
Pyramidal System
Basal Ganglia functions

- 3 Major divisions
  - MOVEMENT
  - COGNITION
  - EMOTION MOTIVATION

  - Sensorymotor via putamen
  - Associative via dorsal caudate
  - Limbic via ventral striatum
Basal Ganglia: Functions

- Movement is modulated by series of excitatory or inhibitory influences
- Lesion will create imbalance of modulation
Basal Ganglia Disorders

- BIOCHEMICAL
- STRUCTURAL
Parkinsonism Classification

1. Primary parkinsonism PD

2. Multisystem degenerations
   ○ MSA, PSP, CBD

3. Heredodegenerative parkinsonism
   ○ Wilson’s disease, neuroacanthocytosis

4. Secondary/acquired parkinsonism
   ○ Post-encephalitic, vascular, drugs
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 forward, and to pass from a walking to a running pace; the senses and intellects being uninjured.
Epidemiology of PD

• Prevalence 0.3% of whole population

• 4% of population over 80y

• Mean age of onset 60y

• 5-10% however young onset between 20y and 40y (early < 40y, juvenile < 20y)
Parkinson Disease

• Neurodegenerative disorder of CNS
Parkinson Disease

• Most sporadic

• Genetic loci PARK1-3 with causative mutations in 6 nuclear genes

AD or AR disorders

• Genetic factors can contribute to PD susceptibility: PARK10 idiopathic late onset disease
Parkinson Disease

Cut section of the midbrain where a portion of the substantia nigra is visible

Substantia nigra

Diminished substantia nigra as seen in Parkinson's disease
Parkinson Disease

Misfolding of alpha synuclein
↓
Lewy Body formation
↓
Cellular oxidative stress
↓
Energy depletion
Parkinson Disease

– Also involved
– ? Earlier affected

Nucleus basalis
LC
Dorsal raphe nucleus
Dorsal vagal nucleus Olfactory bulb
Thalamus
Peripheral sympathetic cell
Neocortical /limbic
Parkinson Disease

- Reduced SN dopaminergic facilitation of the direct pathway
- Inhibition of indirect pathway
Parkinson Disease

• Increased firing and inhibition of the **thalamocortical** pathways
Well, I always wanted to be one of the movers and shakers... I've been diagnosed with Parkinson's.
Motor Symptoms of PD

- Tremor
- Rigidity
- Bradykinesia
- Postural instability
- Forward-flexed posture
- Decreased arm swing
- Mask face
- Small handwriting
Neuropsychiatric features

Cognitive disturbances
- Planning/abstract
- Attention, slowed speed
- Recalling learned information
- Dementia (6 fold increased)

Mood/behaviour problems
- Depression
- Apathy
- Anxiety
- Impulse control

Psychotic symptoms
Other Clinical Features

Sleep
- Fragmentation
- REM disorder
- Daytime

Autonomic
- Hypotension
- Bladder/Constipation
- Sexual

Perception
- Smell

Fatigue

Sensory
- Pain/Paresthesiae
- Numbness
- RLS

Ophthalmologic
- Decreased blink
- Decreased pursuit
- Up gaze
Diagnosis

• Medical history and examination

• Reduction of motor impairment in response to administration of levodopa strong sign pointing to PD

• May be difficult early

• Lewy bodies on autopsy
PD Society Brain Bank criteria

• Bradykinesia plus either Rigidity, resting tremor or postural instability

• Other possible causes need to be ruled out (strokes, head injuries, encephalitis, autonomic symptoms, cerebellar signs, drugs)
PD Society Brain Bank criteria

• Supportive prospective criteria:
  • 3 or more with criteria 1: **Definite PD:**
    – Unilateral onset
    – Resting tremor
    – Progression
    – Asymmetry of motor symptoms
    – Response to levodopa at least 5y
    – Clinical course at least 10y
    – Dyskinesias induced by levodopa
Differential diagnosis

• Postural, action and intention tremors
• Alzheimer’s disease
• Multiple cerebral infarction
• Drug-induced
• Parkinson plus syndromes
Imaging

CT and MRI imaging of patients with pure PD usually appear normal

used to rule out secondary causes of parkinsonism, incl. BG tumours, vascular pathology and hydrocephalus
Imaging

PET and SPECT radiotracers can measure Dopaminergic function

A pattern of reduced Dopaminergic activity in the BG can aid in the diagnosis of the disease
Predict rapid progression

- Early cognitive decline
- Presenting with rigidity or bradykinesia
- Older age of onset
Treatment

At present there is no cure for PD

• Medication, surgery and multidisciplinary management can provide relief from the symptoms
Results from Parkinson's treatment after 1 - 6 months (up to May 2008)

- Deterioration (0)
- No change (1)
- Improvement (2)
- Strong improvement (8)
- Cured (0)

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Treatment of PD

- Increase levels of dopamine in the brain in attempt to slow down disease progression
- Lifestyle modification control motor symptoms in the early stages
- Surgical treatment (DBS)
Novel Approaches in PD

- Neuroprotective (Azilect)
- Foetal cell transport
- Gene therapy
Treatment

• Treatment differ for every person

• Treatment changes as disease progresses

Goal

To provide control of signs and symptoms for as long as possible while minimizing adverse effects
Treatment

Studies demonstrates that disease can deteriorate quickly if treatment is not instituted at/shortly after diagnosis
Early onset disease

MOA-B

Levodopa

Dopamine Agonist

Anti-cholinergic

Amantidine
Advanced disease

Levodopa small dosages more frequently

COMT-inhibitors
Carbidopa-levodopa

Greatest effect

Fewer adverse effect in short term

Long-term side effects

Motor fluctuations \[\rightarrow\] Dyskinesias
Dopamine Agonist

• Symptom relief at lower risk of developing motor complications

Problems

Orthostatic hypotension, sleepiness, hallucinations, edema, pleural effusion, retroperitoneal fibrosis, pathological gambling/sexual behavior, restrictive valvular disease
MAO-B inhibitors

Azilect

Neuroprotective
Deep Brain Stimulation
Deep Brain Stimulation

- Implanted into affected area, with a wire under the skin to battery-operated pulse generator implanted near the collarbone
- Programmed to send continuous electrical pulses to the brain
Deep brain stimulation

The Deep Brain Stimulation system is used to help control tremors and chronic movement disorders. Tiny electrodes are surgically implanted in the brain and are connected via a subcutaneous wire to a neurostimulator (or two, for some diseases) implanted under the skin near the clavicle.

DBS lead
Thin, insulated coiled wires, each ending in a 1.5 mm electrode, that deliver stimulation to the targeted areas.

Neurostimulator
A pacemaker-like device that contains a battery and circuitry to generate electrical signals that are delivered by the leads to the targeted structures deep within the brain.

Extension
An insulated wire that connects the lead to the neurostimulator.

The clinician can program and adjust the settings of the neurostimulator externally via a hand-held device.
Dementia with Lewy Bodies

Prominent disruption of attention and visual spatial abilities
Visual hallucinations
Parkinsonism Depression
Multisystem Atrophy

Include disorders with various combinations of pyramidal, extrapyramidal, cerebellar, autonomic features
Corticobasal Degeneration

- Akinetic rigidity
- Apraxia
- Alien limb
- Cortical sensory loss
- Dystonia and tremor
- Aphasia
- Myoclonus
Huntington’s Disease

- 1/10 000
- Equal sex bias
- AD
- CAG trinucleotide repeat disorder ⇒ worsened disease, earlier onset
Huntington’s Disease

Devastating, progressive movement disorder associated with psychiatric and cognitive decline, leading to a terminal state of dementia and immobility.
Huntington’s Disease

Fragments of huntingtin protein containing expanded polyglutamine may be neurotoxic
Wilson’s Disease

- Hepatolenticular degeneration
- 30/mil
- AR
- Defect of cellular copper export
Wilson’s Disease
Wilson’s Disease

Reduced biliary excretion of copper

Accumulation in liver and other tissue including brain

Hepatic, Neurological, Hematological, Renal impairment