Parkinsonism

- James Parkinson 1816

Parkinsonism

- A syndrome
  - bradykinesia (slowness of movement)
  - rigidity (stiffness of muscles)
  - Tremor (at rest)
  - postural instability (balance difficulty)

Causes of Parkinsonism

- Idiopathic (Parkinson’s Disease)
  - Familial / genetic (rare)
  - sporadic
- Drug induced
- Parkinson’s plus syndrome
  - Multiple System Atrophy (MSA)
  - Progressive Supranuclear Palsy (PSP)
- Miscellaneous
  - hydrocephalus, multiple small strokes, post-encephalitic, repeated head injury, toxins - MPTP, manganese.
PD motor and non-motor symptoms
- Tremor, rigidity, bradykinesia, postural disturbance
  - Autonomic
    - Bladder, constipation, postural hypotension
- Other motor: muscle pain, excessive saliva, low volume voice, swallowing difficulty, small writing, falls, freezing
- Non-motor symptoms
  - Excessive sleepiness, reduced alertness
  - REM-related sleep disorder, restless legs
  - Cognitive problems; memory, hallucinations,

PD - clinical features over time
- Asymmetrical onset
  - Tremor prominent
  - L-dopa responsive
- Variable progression with time
  - Fluctuations in l-dopa response, dyskinesias, —Wearing off.
  - Gait freezing, postural instability
  - Cognitive impairment — memory problems
  - Hallucinations,
  - Excessive sleepiness- fluctuates
  - Sleep attacks during day
  - REM- related sleep disorder

Drug therapy for Parkinson’s Disease

Treatment of Parkinson’s disease
- Diagnosis and counselling
- Drug therapy (dopamine replacement)
  - Non-drug therapies
    - Physical treatments
  - Surgery

Drugs used in PD
- Dopaminergic agents
  - Levodopa + dopa decarboxylase inhib. — Sinemet, Madopar, Stalevo Duodopa
  - Dopamine agonists- ropinerole, pramipexole, cabergoline, rotigotine bromocriptine, apomorphine
- COMT inhibitors- entacapone (Comtess)
- MAO-B inhibitors- selegeline (eldepryl) rasagiline (azilect)
- (Anticholinergics- benzhexol, benzotropine)
- Amantadine (Symmetrel)

L-dopa prolongs survival in PD
**Anticholinergics: one plus, many minuses**

- Useful in a young patient with dominant tremor
- Cause and worsen cognitive problems
  - Hallucinations, delusions
  - Acute confusional state
  - Dementia

**Dopamine agonists: pluses and minuses**

- First drug of choice: mild symptoms in young patient.
- Less dyskinesia but also less effective than L-dopa
- Older dopamine agonists bromocriptine, pergolide and cabergoline are ergot derivatives
  - Cause retroperitoneal fibrosis and cardiac valve fibrosis
- Ropinerole, pramipexole and rotigotine preferred.
  - Rotigotine given by patch - useful for full 24 hrs
  - Dopamine agonists less well tolerated > 70 yrs.
  - Dopamine agonists can cause hypersomnolence hallucinations, delusions, confusion.

**General rules about treatment of PD (1)**

- The gold standard therapy is L-dopa in the form of Sinemet, Madopar or Stalevo.
- Every person is different
  - Therapy is individualised according to you.
- Medication is best taken on an empty stomach
  - better absorbed - quicker action
  - However
    - Some people cannot tolerate medication without food.

**General rules about treatment of PD (2)**

- Yes, you can take 2 different tablets together - for example requip and stalevo
- To get started (on) as soon as possible in the morning, take tablets first thing on wakening,
  - wait in bed for 30 mins until they are working.
- You can adjust the timing of your medication (fine-tune) according to what you think is best

**General rules about treatment of PD (3)**

- When you start treatment you might be taking tablets 2 - 3 times /day.
- With time you may be taking the tablets more frequently.
- The treatment regime may become very complicated.
- Timing reminder devices may be needed.
General rules about treatment of PD (4)

Treatment is mainly by drugs BUT ALSO
- Physiotherapy
- Speech therapy
- Occupational therapy
- Social worker
- Multidisciplinary approach

General rules about treatment of PD (5)

- The Multidisciplinary team
  - YOU
  - neurologist
  - general practitioner
  - PD specialist Nurse
  - Physiotherapist
  - Occupational therapist
  - Speech and Language Therapist
  - Social Worker
  - Public Health Nurse
  - Personal assistant
  - Spouse
  - Drug specialty Nurse (apomorphine, Duodopa)
  - Friends
  - Psychiatrist

Special problems in PD - Problems with sleep at night

- Wakening at night because tablets wear off
  - Unable to turn in bed
  - Use longer acting L-dopa, use a patch (Neupro)
  - Set the alarm to wake you at 3.00 am
  - Wakening to urinate
    - 1) Use anticholinergic 2) use Nordurine
  - REM-related sleep disorder (rivotril)
  - Restless legs (PLMS) - Neupro patch

Special problems in PD - Bladder

- Urgency, frequency.
  - Anti-cholinergic - detrusitol, ditropan, regurin, and others
- Slowness in micturating
  - ? Prostate
  - Alpha blockers- Omnic
  - Occasionally self intermittent catheterisation
- Recurrent urinary tract infections

Special problems in PD - Excessive day-time sleepiness

- Is it due to night-time sleep disturbance?
  - Snoring? Obstructive sleep apnoea ?
  - frequent waking due to "offs", bladder, restless legs

- May be seen in particular with the dopamine agonist drugs
  - Mirapexin, Requip

- Stop the drugs?
- Use a stimulant - Provigil?
Special problems in PD - constipation
• Due to the PD
• May be an early symptom of PD (even mild)
  • Diet
  • Exercise
  • Fluid
  • Purgatives - many types
    — movicol & codalax very effective

Special problems in PD - Hallucinations
• Formed hallucinations
• People, animals
• Not frightening
• Insight maintained usually
• Tend to occur in the evening
• May co-exist with illusions

Special problems in PD - Hallucinations (2)
• Can occur as a side-effect of medication
• May be a sign of mild cognitive problems
• Respond very well to cholinesterase inhibitors
  • Exelon
  • Aricept
  • Reminyl
• These drugs also improve memory function

Special problems in PD - Cognitive problems
• May be seen in up to 25% patients
• After PD of 10+ years duration
• Short term memory difficulty
• May be associated with reduced alertness
• Fluctuates during the day
• May be accompanied by hallucinations
• Responds well to choline esterase inhibitors

Special problems in PD - pain
• Muscle pain and aching in joints may be a presenting symptom of PD.
• Responds well to dopamine therapy

• Capsulitis of shoulder may complicate the rigidity of PD
• Physiotherapy
• Exercise
• Non-steroidal anti-inflammatory drugs
• Steroid injections into joints

Special problems in PD - depression
• Depression is common in PD
• Not just a reaction to a chronic illness
• Use SSRI drugs (avoid tricyclics)
  • Cipramil
  • Seroxat
  • Efexor

• Stay on the antidepressants 3-6 months
Special problems in PD - excessive saliva

- Sialorrhoea
- Due to reduced swallowing rate in PD
- Not due to excess saliva

- Treatment with botulinum toxin injections into salivary glands
  submandibular & parotid glands
  every 3 - 4 months
  Occasionally atropine patch (but - confusion)

Nonpharmacologic Treatments

- Patient/caregiver education
- Physical therapy
- Exercise
- Occupational therapy
- Speech/language therapy
- Diet and nutrition
- Psychosocial interventions

Future drug therapy

- Neuroprotective agents
  - coenzyme Q10
  - Rasagline (Azilect)
  - selegiline (eldepryl)
  - Safanamide
  - Vitamin E
  - Minocycline
  - Non-steroidal anti-inflammatory drugs
  - GDNF
  - Antagonists of A_{2A} receptors

PD - a synucleinopathy

- a dopamine deficiency disorder in the brain
- Degeneration of cells in the substantia nigra in the mid-brain and locus coeruleus
- Lewy bodies
  - intracytoplasmic contain synuclein
  - Found in SN pars compacta, also cortex
  - Function of synuclein unknown

What causes Parkinson’s Disease?

- Environment
  - MPTP, manganese, well water
- Genes (minor role)
  - Autosomal Dominant
    - α-synuclein, UCHL1, NR4A2, LRRK2
  - Autosomal Recessive
  - Parkin, DJ-1, Pink1
- Unknown agents
Progressive supranuclear palsy (PSP)
- Symmetrical, no tremor, axial rigidity, gait disorder prominent, frequent falls,
- Pseudobulbar palsy
- Eye movement disorder- supranuclear- doll’s head response
- Minimal/no response to L-dopa, progressive restriction & incr falls
- Life expectancy 10-12 yrs

Treatment of Parkinson’s disease
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  - Physical treatments
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L-dopa
- Most effective drug for parkinsonian symptoms
  - First developed in the late 1960s; rapidly became the drug of choice for PD
  - Large neutral amino acid; requires active transport across the gut-blood and blood-brain barriers
  - Rapid peripheral decarboxylation to dopamine without a decarboxylase inhibitor (DCIs: carbidopa, benserazide)
- Side effects: nausea, postural hypotension, dyskinesias, motor fluctuations

Problems with L-dopa
- Dyskinesias
- Wearing off
- Freezing episodes
- On-off fluctuations
- Hallucinations, delusions

Drug management of PD
- Start with dopamine agonists± selegeline
- Add L-dopa later
- Keep anticholinergics to a minimum
- Apomorphine for fluctuations
- Cholinesterase inhibitors for hallucinations and memory problems
- Deep brain stimulation

The Surgical Treatment of Parkinson’s Disease

Part 6 of 7
Deep Brain Stimulation (DBS)
- High frequency, pulsatile, bipolar electrical stimulation
- Stereotactically placed into target nucleus
- Can be activated and deactivated with an external magnet
- Exact physiology unknown, but higher frequencies mimic cellular ablation, not stimulation

Globus Pallidus internus DBS
- Effects tend to mimic those of pallidotomy
- Significant improvement in dyskinesia
- Moderate improvement in cardinal "off" signs
- Bilateral DBS is better tolerated than bilateral pallidotomy
- AE: surgical complications

Cell Transplants
- Autologous adrenal cells
  - Not effective
- Other dopaminergic (retinal) human fetal cells
  - Trials ongoing
- Xenogenic fetal transplant (porcine and bovine)
  - Trials continue
- Genetically engineered / Stem cells
  - Research ongoing

PD motor and non-motor symptoms
- Tremor, rigidity, bradykinesia, postural disturbance

  - Other motor:
    - Muscle pain, arthralgia, micrographia, salivary, dysphagia, hypomimia, hyponoia, dystonic cramps.
  - Autonomic
    - Bladder, constipation, postural hypotension
  - Non-motor symptoms
    - Hypersomnolence, reduced alertness
    - Cognitive problems; initially memory, progressing to hallucinations, delusions.
    - Restless legs, periodic leg movements.
    - REM related sleep disorder
Problems That May Respond to Nonpharmacological Approaches

- Motor, balance, posture, gait, mobility
- ADL difficulties
- Speech and swallowing: hypophonia, sialorrhea, dysphagia
- Inadequate nutrition
- Sleep disturbance
- Autonomic dysfunction: pain and constipation
- Skin breakdown
- Sexual dysfunction
- Depression

Problems That May Respond to Nonpharmacological Approaches (continued)

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PD - clinical features over time

- Asymmetrical onset
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  - Gait freezing, postural instability
  - Cognitive impairment - 25% after 5 years
  - Hallucinations, diurnal variation in alertness, may progress to dementia (Lewy body dementia)

Physical Therapy: Goals

- Maintain or increase activity level
- Decrease rigidity and bradykinesia
- Facilitate movement and flexibility; optimize gait
- Maximize gross motor coordination and balance
- Maximize independence, safety, function

Physical Therapy: Features

- Exercise: e.g., walking (1+ mile/day), swimming, golf, dancing
- Stretching and strengthening
- Exaggerated or patterned movements
  - High stepping, weight shifting, repetition, verbal cues
- Mobility aids, orthotics, adaptive footwear
- Transfer techniques

Occupational Therapy: Features

- Patient and caregiver education
  - Goals of program
  - Transfers, task simplification, positioning, etc.
- Home exercise program
- Home and workplace modifications
- Adaptive equipment
- Upper extremity splinting

Multiple system atrophy

- Parkinsonism, cerebellar & autonomic
- Symmetrical limb - no tremor
- No/minimal L-dopa response
- Prominent autonomic degeneration
  - Severe postural hypotension, atonic bladder
  - Cerebellar + brain-stem atrophy
- May present and remain as mainly one system
- Rarely abductor laryngeal palsy
**Occupational Therapy: Goals**

- Maximize independence, safety, function
- Improve endurance, reduce energy expenditure
- Improve body image, self-esteem, psychosocial adjustment
- Facilitate active movement
- Maximize fine motor coordination
- Increase trunk flexibility and upright posture

**Adaptive Equipment and Environmental Modifications**

- Customize for disability, budget
- Seating: wheelchairs, cushions, lateral supports, etc.
- Toilet and hygiene: tub/shower seat, grab bars, etc.
- Feeding: wide-handled utensils, sip cups, etc.
- Clothing: velcro, pullovers, shoehorns, etc.
- Bed: rails, hospital bed, trapeze, etc.
- Equipment: book holders, large-button phone, key holders, etc.
- Consider door sills, throw rugs, other obstructions

**Techniques to Improve Speech**

- Increase loudness
- Face the listener directly
- Emphasize key words
- Use short sentences
- Range-of-motion exercises for muscles of speech
- Breathing exercises
- Attend speech therapy
Genes and PD: Park 8

- AD families mapped on Chr12 in 2002
- Gene LRRK2
- Product dardarin (dardara- to shake- Basque)
- Seen in 5% familial and in sporadics
- Onset 35-78 yrs, variable expression from typical to cortical LBD: even Tau pathology.
- Reduced penetrance

Movement disorders

- Hyperkinetic
  - chorea
  - dystonia
  - athetosis
  - tics
  - myoclonus
- Hypokinetic
  - Parkinsonism
  - Stiff-person syndrome

PD- epidemiology

- Incidence
  - 24 / 10^5 worldwide. Incidence of PD rising slowly with aging population
- Prevalence
  - 300 / 10^5 worldwide
  - 35%-42% of cases undiagnosed at any time
- Onset
  - mean 62.4 years
  - rare before age 30; 4-10% cases before age 40
Convergence of function in patients with Parkinson disease (PD)

Kaplan-Meier Survival Curves for 159 Persons with Parkinsonism — 128 Who Had Gait Disturbance and 31 Who Did Not — and for 301 Persons without Parkinsonism through Eight Years of Follow-up