Parkinson’s disease – Current Research and Future Developments

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Overview

• Introduction to Parkinson’s
• Current Treatment strategies
• New developments/research
• Non Motor Symptoms
• The future
James Parkinson

- He noted:
  - ‘Involuntary tremulous motion’
  - ‘A propensity to bend forwards’
  - ‘The senses and intellect are intact’
Parkinson’s Defined

• Parkinson’s is:
  – A chronic, progressive, neurological degenerative disease

• The contemporary definition is:
  – ‘Multi-system neurological disorder which affects cognitive processes, emotion and autonomic function.’
Aetiology of Parkinson’s

- Incidence of Parkinson’s is 4-20 per 100,000 per year\(^{(3)}\)
- Prevalence of Parkinson’s may be up to 200 per 100,000\(^{(3i)}\)
- There are approximately 120,000 people with Parkinson’s in the UK\(^{(3ii)}\)
  - Almost a quarter are in hospital or residential care
  - Almost a third in the community requiring help
  - Nearly half are independent, living in the community
- Age at onset is 30+, usually 50+\(^{(4)}\)
The Cause of Parkinson’s

• In most cases, the cause of Parkinson’s is unknown
  – Age
    • The ageing process is intricately linked to Parkinson’s, but is not solely responsible
  – Genes
    • Parkinson’s inheritance is rare (5)
  – Environment
  – Genes plus environment
Normal Movement
Dopamine

Striatal dopamine receptors

Activated receptor

Striatal neurone

Nerve terminals

Normal neuronal function
Parkinsonian State
Striatal dopamine receptors

Activated receptor

Unactivated receptor

Normal neuronal function

Dopamine

Striatal neurone

rostriatal nerve terminals

rostriatal nerve terminals
Diagnosis

- Based on clinical presentation:
  - Bradykinesia
  - Rigidity
  - Tremor
  - Postural Instability
The four clinical management stages

There are four stages of management for PD

1. Diagnosis phase
2. Maintenance phase
3. Complex phase
4. Palliative phase
Current Therapeutic strategies

1. Increase dopamine levels in the brain
   *(Sinemet, Madopar)*

2. Metabolism and breakdown of dopamine in the brain
   *(Selegiline, Rasagiline, Entacapone, Tolcapone)*

3. Stimulate dopamine receptors
   *(Pergolide, Cabergoline, Ropinirole, Rotigotine, Pramipexole, apomorphine)*
Levodopa Therapy

• Most effective drug for treating Parkinsons Disease
  – E.g. Sinemet, Madopar

• Long term use is complicated by significantly disabling fluctuations and dyskinesias
Dyskinesia

- involuntary fidgety movements can include twitches, jerks, twisting or writhing movements or simple restlessness
- can take the form of rapid dance like movements – known as ‘chorea’
  - loose and floppy muscles and too much movement
- or dystonia
  - a sustained involuntary contraction of the muscles causing the affected part of the body to go into spasm

- Typically occur at the peak of levodopa dose, but can also occur at the beginning or end of the dose interval
Long-term challenges: Changes in levodopa response

Obeso et al. 2000
Optimising Levodopa Therapy

• Improve consistency of absorption
  – Treatments to improve gastric emptying
    • E.g. Reviewing medications which can slow gastric emptying
    • Treating constipation
    – Taking doses one hour before or after meals
• Use smaller doses more frequently
• Consider the use of modified release preparations
Dopamine agonists

- Ergot
  - Bromocriptine
  - Lisuride
  - Cabergoline
  - Pergolide

- Non ergot
  - Apomorphine
  - Ropinirole
  - Pramipexole
  - Rotigotine (patch)
Long term challenges: Dopamine agonists

- Fibrotic reactions (ergot derived)
  - Retroperitoneal, pleuropulmonary, cardiac
- Neuropsychiatric symptoms
  - Impulse control disorders
    - Compulsive gambling
    - Punding
- Sudden onset sleep
  - (?all dopaminergic agents)
Complications of missed/late doses

• Ability to manage symptoms may be lost
  – Reduced mobility
  – Increased risk of aspiration

• Can be as serious as neuroleptic malignant syndrome
  – Fevers, confusion

• ‘Get it On Time Every Time’
Advancing strategies

• Continuous delivery of medication for continuous, stable blood levels & effect

• Examples
  – Dopamine agonists
    • Rotigotine Patch (Neupro®)
    • Controlled release pramipexole/ropinirole
    • Apomorphine infusion
  
  – Levodopa intestinal gel (Duodopa®)
In PD, pulsatile delivery of traditional levodopa leads to pulsatile stimulation of dopamine receptors.

- **Activated**

- **Unactivated**

**PD (untreated)**

**Normal**

**Traditional levodopa**

- **Activated**
- **Unactivated**

**Striatum**

**Substantia nigra**
Duodopa®

- Continuous infusion of levodopa/carbidopa administered with a portable pump directly into the duodenum or upper jejunum
- Surgical procedure for Percutaneous endoscopic gastrostomy tube insertion
- Pump is then programmed to deliver dose at an individualised rate
Surgical Intervention

- Deep Brain Stimulation
  - Electrodes in basal ganglia targets
  - Contra-indications in cognitive decline/neuropsychiatric problems

- Pallidotomy for severe dyskinesia
- Lesional surgery where DBS not possible
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Non-Motor Features of Parkinson’s

- Cognitive deficiencies
- Depression
- Raised anxiety levels
- Olfactory deficiencies (smell and taste)
- Sleep disturbance
- Fatigue
- Pain
- Bowel and bladder problems
- Sexual dysfunction
Depression and Anxiety

• Depression
  – Can affect up to 45% of patients
  – Positive results from small studies using dopamine agonists e.g. pramipexole and ropinirole XL
    – effects of dopamine stimulation on mood
    – Improvement of motor control
  – CBT – Cognitive Behavioural Therapy
  – Antidepressant therapy

• Anxiety
  – Often coexists with depression
    • Can be responsive to antidepressant therapy (as above)
  – Can be dopamine dependent
    • E.g. panic attacks when ‘levodopa wearing off’
Sleep Dysfunction

- Dopamine has a complex role in the sleep/wake cycle
- Insomnia
  - Difficulty falling asleep
  - Difficulty maintaining sleep
- Possible treatments
  - Good sleep hygiene
  - Slow release levodopa formulation
    - To improve ‘off’ state symptoms disturbing sleep
  - Other agents to improve sleep quality
Recent/Current Research

• Continuous Stimulation

• Neuroprotection
  – Early versus late treatment

• Impact and treatment of NMS
  – Europar
The Future

• Neurorestoration

• Gene therapy

• Nerve cell transplantation
Parkinson’s disease

Diagnosis and management in primary and secondary care

NICE clinical guideline 35
References

(2) Playfer J, et al. (2001), Parkinson’s Disease in the Older Patient. Arnold, London
(3) Clough C et al. (2003), Parkinson’s Disease, Health Press Ltd. Oxford
(4) Quinn N. (1997), Parkinson’s Disease: Clinical Features. Balliere’s Clinical Neurology: 6 (1) 1-16
(9) Aquilonius S et al; Parkinson’s disease – role of continuous dopaminergic stimulation; ESP Bioscience Ltd; 2012
ELLDOPA trial

NEJM 2004;351:2498
The role of dopamine

- Dopamine acts to oppose acetylcholine
- Dopamine inhibitory
- Acetylcholine excitatory
- Depletion in dopamine results in hypokinetic disorders such as PD
Parkinson’s Risk Factors

- **Definite risk factors**
  - Age

- **Highly likely risk factors**
  - MZ co-twin with early-onset Parkinson’s

- **Probable risk factors**
  - Positive family history

- **Possible risk factors**
  - Herbicides / pesticides
  - Heavy metals
  - Proximity to industry
  - Farming communities
  - Repeated head trauma

- **Possible protective effect**
  - Smoking and dopamine agonists
Signs and Symptoms

• **Impairment of postural reflexes**
  – Usually later onset in PD, but earlier onset in Parkinsonism
  – Combined with other features, it leads to a high risk of falls

• Other features – insidious onset, initially unilateral symptoms
Management options for specific motor fluctuations

- **‘Wearing off’**
  - Shorten dosage interval
  - Pre meal levodopa
  - Addition of a COMT inhibitor or dopamine agonist
  - Controlled release levodopa before sleep
  - Addition of a MOA-B inhibitor

- **Early morning dystonia**
  - Late evening or night time dose of controlled release levodopa
  - Addition of a long acting dopamine agonist

- **Dyskinesia**
  - Amantadine at high doses has an antidyskinetic action which may last up to 9 months without affecting Parkinson’s control
Metabolism of L-dopa
Signs and symptoms cont

- **Facial**
  - Impassivity, poverty of blinking
- **Speech**
  - Monotonous, hypophonic
- **Movement**
  - Decreased manual dexterity, rigid hands & arms ‘frozen shoulder’
- Olfactory abnormalities
- Bulbar symptoms