Parkinson’s disease

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Dr. James Parkinson

English apothecary surgeon, geologist, paleontologist, and political activist. In 1817 he described 6 people with “paralysis agitans” in “An Essay on the Shaking Palsy”.

Dr. J.M. Charcot named the condition as Parkinson’s disease 60 years later.
Parkinson’s Disease

Progressive neurodegenerative disorder with motor but also complex non-motor and psychiatric features.

Prevalence: 100-200 per 100,000 in people over 40 y
350 per 100,000 in people over 85 y old
mean age at diagnosis is 70 y
5,000,000 patients worldwide

10-25% have at least one first degree relative with PD
Dopaminergic neurons originating in the substantia nigra and projecting from substantia nigra to striatum and cortex degenerate.

There are approximately 400,000 neurons with extensive projections.

Each dopaminergic neuron has approximately 500,000 synapses.

Dopaminergic neurons deliver dopamine = one of main neurotransmitters of reward and motivation.
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- Dopamine
- Components of reward system are “liking” and “wanting”. While liking is closer to sensory systems, wanting is closer to motor actions.
- Neurologically, wanting is intimately linked to the mesolimbic dopamine system, which is crucial for the orchestration of motor behavior to obtain rewards. Dopaminergic projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex are the most important component of the implicit or unconscious "wanting" system

H. Zheng, Physiology, 2007
Parkinson’s disease

Pathologic hallmark is **Lewy Body** - found in substantia nigra (Parkinson’s disease), cortex (Parkinson’s with dementia) but also in myenteric plexus of intestines and cardiac sympathetic plexus.
Parkinson’s Disease

Jose A Obeso, Nature Medicine, Vol. 16, p 653-661, 2010
Basal Ganglia
Clinical diagnosis

Based on the following features:

1. Tremor
2. Rigidity
3. Bradykinesia
4. Postural instability
Parkinson’s disease
1. Tremor

- 1) tremor frequency varies in different body parts,
- 2) tremor amplitude and frequency are inversely related
- 3) the tremor of Parkinson’s disease is a relatively low-frequency rest tremor, suppressed by action, and generally synchronous in symmetric body parts, but varying in amplitude and frequency in different body parts or over time.

(PD trace 2-6: 3-7 Hz, MS trace 7, hysteria trace 9)

- Usually unilateral, spreads, aggravated by mental exercise, rarely involves head.
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2- Bradykinesia

- Main cause of disability
- Slowness, decreased ability to initiate movement, “weakness”
- In arms starts distally with loss of dexterity
- In legs presents with dragging legs, shuffling gait
- Reduced rapid movements (finger tapping, foot tapping)
- Reduced blinking rate
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3- Rigidity

- Increased resistance to passive movement about a joint (cogwheel or lead-pipe rigidity)
  (spasticity is a pyramidal sign and calls for other pyramidal signs like hyperrelexia and upgoing toe)

- Cause of stiffness and pain
- “striatal hand “ sign
- Decreased arm swing, stooped posture

- Can be facilitated by having patient perform mental exercise or active movement in contralateral limb
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4- Postural instability

- Impairment of centrally-mediated postural reflexes
- Late sign
- Major cause of disability
- Most difficult to treat (reflects cholinergic deficit in thalamus, not dopaminergic deficit)
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- Clinical subtypes
  - 1. Tremor predominant
  - 2. Akinetic – rigid type
  - 3. Postural instability and impaired gait predominant

- Accuracy of diagnosis is 75% based on exam, 90% with long-term follow up
Parkinson’s disease

Other motor symptoms (some with parkinsonism)

- **Craniofacial** (hypomimia, decreased blinking rate, hypophonia, hypokinetic dysarthria, palilalia, dysphagia, sialorhea)

- **Musculoskeletal** (micrographia, dystonia, myoclonus, stooped posture, camptocormia, kyphosis, scoliosis, difficulty turning in bed)

- **Gait** (shuffling, short-stepped gait, freezing, festination)

- **Visual** (hypometric saccades, impaired vestibuloocular reflex, eyelid opening apraxia, impaired contrast sensitivity, blurry vision, impaired convergence and upgaze)
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Non-motor clinical symptoms

- Cognitive dysfunction and dementia
- Psychosis and hallucinations
- Mood disorders including depression, anxiety, and apathy/abulia
- Sleep disturbances
- Fatigue
- Autonomic dysfunction
- Olfactory dysfunction
- Pain and sensory disturbances
- Dermatologic findings (seborrhea)
- Polyneuropathy
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Differential diagnosis

- **Essential tremor**

- **Parkinsonism** (Lewy body disease, Multiple system atrophy, Progressive supranuclear palsy, Corticobasal degeneration) Sometimes it may be years before atypical features occur and the diagnosis changes from PD to atypical parkinsonism.

- Other neurodegenerative diseases (Alzheimer’s).

- **Secondary parkinsonism** (order CT brain, blood tests to r/o)
  - vascular: small vessel disease,
  - drug-induced: antinauseants, antipsychotics
  - toxic: CO, organic solvents, MPTP
  - metabolic disorder: Wilson’s, hypo-parathyroidism
  - Infection: PML, neurosyphilis, AIDS;
  - structural lesions: tumor, hydrocephalus
  - trauma
Can neuro-imaging help with diagnosis? (fMRI, PET scan)
Parkinson’s disease

1. Pharmacological - neuroprotective
   - symptomatic

2. Nonpharmacologic (exercise, education, nutrition, support, safety)

3. Surgical (DBS, pallidotomy, stem cells, gene therapy)
Parkinson’s disease
Therapy
Parkinson’s disease
Therapy
Parkinson’s disease
Therapy

- **Substantia Nigra**
  - rasagiline
  - selegiline
  - amantadine
- **Blood Brain Barrier**
  - levodopa
  - carbidopa
  - benserazide
  - tolcapone
  - entacapone

- **Dopamine agonists**
  - bromocriptine
  - pergolide
  - pramipexole
  - ropinirole

- **Striatum**
  - baclofen
  - trihexyphenidyl
  - DA
  - GABA
  - ACh
Parkinson’s disease
Pharmacotherapy

- **Levodopa** (Sinemet, Sinemet CR, Prolopa, Stalevo)
- **Dopamine agonists:**
  - Pramipexole (Mirapex) start at 0.125 mg t.i.d., increase slowly up to 1 mg t.i.d. or 1.5 mg t.i.d.
  - Ropinirole (Requip) start at 0.25 mg t.i.d. increase slowly up to 5-7 mg t.i.d.
  - Bromocriptine (Parlodel) 2.5 mg daily increase slowly up to 5-10 mg t.i.d.
  - Rotigotine patch (temporarily not available)
- **MAO B inhibitors:**
  - Selegiline (Deprenyl) 5 mg daily
  - Rasagiline (Azilect) 0.5-1 mg daily
- **COMT inhibitors:**
  - Entacapone (Comtan) 200 mg with each Sinemet (up to 600-800 mg daily)
  - Tolcapone (Tasmar) not available
- **Anticholinergic agents:**
  - Trihexyphenidyl (Artane) 1 mg b.i.d. up to 2 mg t.i.d.
  - Amantadine (Symmetrel) – 100 mg daily, up to 100 mg t.i.d.
Do we have a neuroprotective drug? (rasagiline? Coenzyme Q10 300-1200mg?levodopa?)

- Start pharmacotherapy when symptoms start to impact activity of daily living regardless if patient has typical or atypical features of PD
- levodopa or dopamine agonist?
- if levodopa: levodopa/carbidopa CR 100/25: ½ to 1 tab. t.i.d., usual dose is 300 to 600 mg levodopa per day.
- Motor fluctuations (50% of patients after 5 years of treatment) are more common in young onset PD, large dose of levodopa
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Pharmacotherapy

- **Motor Complications**
  - Wearing off
  - Delay to turning on
  - On-off periods
  - Dyskinesias
  - Dystonia
  - Freezing
  - Falling
Parkinson’s disease
Pharmacotherapy

Treat "off" time

- 2006 AAN Guideline Recommendations For Treating "Off" Time — An evidenced-based practice parameter
- Entacapone and rasagiline are established as effective and should be offered to reduce "off" time. Pramipexole, ropinirole, and tolcapone are probably effective and should be considered to reduce "off" time, with the stipulation that the adverse effects of tolcapone (hepatotoxicity) requires monitoring. Apomorphine, cabergoline, and selegiline are possibly effective and may be considered to reduce "off" time. Sustained release carbidopa-levodopa does not decrease "off" time compared with immediate release carbidopa-levodopa; bromocriptine does not reduce "off" time compared with placebo.

General suggestions:
- Add a DA
- Add a COMT inhibitor
- Increase dose of dopaminergic therapy
- Substitute sustained-release levodopa
- Adjust diet
- Adjust timing of drug
- Increase gastric motility (domperidone 10 mg)

- ? Helicobacter eradication
2006 AAN Guideline Recommendations For Reducing Dyskinesia

An evidenced-based practice parameter: Amantadine is possibly effective and may be considered for reducing dyskinesia. There is insufficient evidence to support or refute the effectiveness of clozapine in reducing dyskinesia.

Levetiracetam (500-1000mg) is possibly effective.

General suggestions:
- Lower the levodopa dose when possible
- Replace a portion of the levodopa dose with a dopamine agonist, if necessary
- Replace sustained-release levodopa with regular levodopa, if dyskinesia is occurring in the late afternoon and evening
- Add amantadine to counteract dyskinesia
- Manage diphasic dyskinesia with more frequent levodopa dosing
- Use middle-of-the-night levodopa or a dopamine agonist to treat early morning "off" period dystonia
- Reduce the levodopa dose intervals or add a DA to treat "off" period dystonia during the day
Parkinson’s disease: complications

- **Dopamine dysregulation syndrome**
  - Compulsive use of dopaminergic drugs
  - DDS typically involves male patients with early onset PD who take increasing quantities of dopaminergic drugs despite increasingly severe drug-induced dyskinesia
  - Punding—a form of complex, prolonged, purposeless, and stereotyped behavior
  - associated with a cyclical mood disorder characterized by hypomania or manic psychosis. Tolerance and a withdrawal state occurs with dose reduction or withdrawal.
  - ! Avoid “rescue” levodopa

- **Impulse control disorders** including hypersexuality and pathologic gambling, shopping may occur
  - ! Avoid dopamine agonists and amantadine
Parkinson’s disease
Non – Pharmacological therapy

- **Education**
- **Support**  (http://www.wemove.org/)
- **Exercise**  - Multidisciplinary rehabilitation with standard physical and occupational therapy components
  - Treadmill training with body weight support
  - Balance training and high-intensity resistance training
  - Cued exercises with visual (mirror), auditory (metronome), and tactile feedback
  - Active music therapy
  - Speech and voice therapy
Psychosis and hallucinations (Seroquel start with 12.5-25 mg OD and increase as tolerated, Clozaril, cholinesterase inhibitors, electroshock therapy in refractory cases—may improve also motor symptoms)

Mood disorders:
Depression (increase dopaminergics, SSRI, SNRI, TCA, Mirtazapine – can improve tremor)
Anxiety (reduce dopaminergics in agitation, minimize benzodiazepines)
Apathy/abulia (increase dopaminergics, stimulants—modafinil; cholinesterase inhibitors)
Sleep disturbances (melatonin, Zopiclone, HRT?)
Fatigue (amantadine)
Autonomic dysfunction (fludrocortisone)
Olfactory dysfunction
Pain and sensory disturbances (gabapentin, pregabalin)
Dermatologic findings (seborrhea)
Polyneuropathy (symptomatic therapy)
Cognitive dysfunction and dementia (cholinesterase inhibitors)
Parkinson’s disease
Surgical therapy

- Pallidotomy
- Thalamotomy

(now replaced with DBS)
Parkinson’s disease
Deep Brain Stimulation
Cell replacement therapy (CRT) offers great promise as the future of regenerative medicine in Parkinson’s disease (PD). Three decades of experiments have accumulated a wealth of knowledge regarding the replacement of dying neurons by new and healthy dopaminergic neurons transplanted into the brains of animal models and affected patients. The first clinical trials provided the proof of principle for CRT in PD. In these experiments, intrastriatal transplantation of human embryonic mesencephalic tissue reinnervated the striatum, restored dopamine levels and showed motor improvements. Sequential controlled studies highlighted several problems that should be addressed prior to the wide application of CRT for PD patients. Moreover, owing to ethical and practical problems, embryonic stem cells require replacement by better-suited stem cells. Several obstacles remain to be surpassed, including identifying the best source of stem cells for A9 dopaminergic neuron generation, eliminating the risk of tumor formation and the development of graft-induced dyskinesias, and standardizing dopaminergic cell production in order to enable clinical application.
Parkinson’s disease
Management
(AAN recommendations 2011)

- 10 Parkinsons’ disease measures
  - 1. Annual PD diagnosis review
  - 2. Psychiatric disorders or disturbances assessment
  - 3. Cognitive impairments or dysfunction assessment
  - 4. Querying about symptoms of autonomic dysfunction
  - 5. Querying about sleep dysfunction
  - 6. Querying about falls
  - 7. PD rehabilitative therapy options
  - 8. Counseling on PD-related safety issues
  - 9. Querying about PD medication-related motor complications
  - 10. Review of PD medical and surgical treatment options
Parkinson’s disease
When to refer to specialist

• “Patients with suspected mild disease should be seen within six weeks, while new referrals with more advanced disease and more complex problems should be given a specialist appointment within two weeks”. *BMJ.* 2006 July 1; 333(7557)

• 1. Early stage: if not sure about diagnosis (is it PD?)
• 2. Middle stage: if poorly controlled
• 3. Late stage: if there are atypical features.

• Patient complaints of tremor (you are not sure what type of tremor it is)
• Patient complaints of stiffness and loss of dexterity in hand
• Patient complaints of shuffling gait, dragging legs behind
• Patient complaints of micrographia
• Patient looks parkinsonian and has unusual features:
  - Symmetric signs
  - Lack of tremor
  - Falls early in disease
  - Autonomic dysfunction early in disease
  - Poor response to levodopa
  - Dementia early in disease
Parkinson’s disease
conclusions:

- Neurodegenerative disorder with motor and non-motor symptoms
- Diagnosis is based on clinical signs of rest tremor, rigidity, bradykinesia and postural instability
- There is no readily available diagnostic test, investigations are done to r/o other conditions
- Therapy is pharmacological, non-pharmacological and surgical
- So far there is no proven neuroprotective drug
- It is better to start pharmacotherapy slowly and to stay with lowest effective doses
- Non-pharmacological therapy (exercise) can greatly improve motor symptoms and can improve balance
- Surgical therapy is an option in selected patients
- It is important to monitor patients over time and watch for complications and any new atypical signs
Thank you.

Feel free to e-mail me if you have any questions.