Hypokineti

c Movement Disorders

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Hypokinetic movement disorders

• Diminished voluntary movement unrelated to weakness or spasticity

• The most common of these disorders is forms of “parkinsonism”

Photo by Arthur Londe from Nouvelle
Iconographie de la Salpêtrière, vol. 5., p.226
**Classification of parkinsonism**

<table>
<thead>
<tr>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Parkinson's disease</td>
</tr>
<tr>
<td>• Juvenile parkinsonism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infectious</td>
</tr>
<tr>
<td>• Drugs</td>
</tr>
<tr>
<td>• Toxins</td>
</tr>
<tr>
<td>• Vascular</td>
</tr>
<tr>
<td>• Trauma</td>
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<tr>
<td>• Metabolic</td>
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</tbody>
</table>

**Atypical parkinsonian syndromes**

- Corticobasal degeneration (CBD)
- Progressive Supranuclear Palsy (PSP)
- Multiple System Atrophy (MSA)
- Lewy Body Dementia (LBD)

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**Parkinson’s Disease**

- Second most common neurodegenerative condition next to Alzheimer's Disease
- 1%-2% of people over 60
- Rare before 50
- Prevalence increases with age
  - Up to 4% in the highest age groups
- In the United States
  - 630,000 people diagnosed in 2010
  - Prevalence likely to double by 2040
- In 2010 national economic burden of PD > $14.4 billion

De Lau LM, Breteler MM. Lancet Neurol 2006
Kowal, SL. Dall, TM et al. Mov Disorders 2013
### Pathologic hallmarks

| Loss of dopaminergic neurons primarily in substantia nigra pars compacta |
| - By the time symptoms appear, SN has lost 60% of DA neurons and DA content of striatum is 80% of normal |
| Proteinaceous inclusions in nerve cells and terminals, known as Lewy bodies and Lewy neurites respectively |
| - Alpha-synuclein major component |
| Glial response in all area of brain where signs of neurodegeneration can be found |

### Diagnostic testing

| In life, defined by clinical findings |
| No diagnostic lab/imaging tests |
| - Insufficient evidence that urodynamics, autonomic testing, EMG, MRI, sonography and PET scanning is useful in differentiating PD from other forms of parkinsonism |
| Levadopa challenge |
**DaTscan**

[$^{[123]}$FP-CIT SPECT scan]

- 2011 FDA approved to distinguish essential tremor vs parkinsonism
- Measures activity of dopamine transporter (DaT)
- Does NOT diagnose PD - Adjunct to patient workup to supplement, and not replace, neurological examination and clinical judgment
- PD, PSP, MSA and other parkinsonian syndromes all abnormal
- Needs trained interpreter

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**UK Brain Bank criteria**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Supportive criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bradykinesia</strong></td>
<td>• Unilateral onset</td>
</tr>
<tr>
<td><strong>At least one of the following:</strong></td>
<td>• Persistent asymmetry affecting side of onset most</td>
</tr>
<tr>
<td>- Muscular rigidity</td>
<td>• Rest tremor present</td>
</tr>
<tr>
<td>- 4-6Hz rest tremor</td>
<td>• Progressive disorder</td>
</tr>
<tr>
<td>- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction</td>
<td>• Excellent response (70-100%) to levodopa</td>
</tr>
<tr>
<td></td>
<td>• Levodopa-induced chorea</td>
</tr>
<tr>
<td></td>
<td>• Levodopa response for 5 yrs or more</td>
</tr>
<tr>
<td></td>
<td>• Clinical course of 10 yrs or more</td>
</tr>
</tbody>
</table>

**Exclusion criteria for PD**

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Neuroleptic treatment at onset of symptoms
- Sustained remission
- Strictly unilateral features after 3 yrs

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**Exclusion criteria for PD**

- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Presence of cerebral tumor or communicating hydrocephalus on imaging
- MPTP exposure
### Rest tremor
- Presents at rest and usually improves when affected limb performs a motor task.
- In 75% of pts is first motor manifestation.
- Usually begins unilaterally.
- Can occur intermittently and vary in intensity.

### Rigidity
- Increased resistance to passive movement of limb segment.

### Bradykinesia
- Early may be confined to distal muscles.
- Later have difficulty rising from chair and generalized slowing of voluntary movements.
- Facial, vocal and cognitive manifestations.
Balance and gait problems

- Earliest sign is often decreased arm swing
- Gait initiation and turning can become difficult
- Freezing can occur when starting to walk, attempting to turn or approaching narrow and crowded spaces
Non-motor features

<table>
<thead>
<tr>
<th>Neuropsychiatric symptoms</th>
<th>-Sleep disturbances</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dementia</td>
<td>• REM sleep disturbances</td>
</tr>
<tr>
<td>• Depression</td>
<td>• Sleep fragmentation</td>
</tr>
<tr>
<td>• Anhedonia</td>
<td>• Excessive daytime sleepiness</td>
</tr>
<tr>
<td>• Apathy</td>
<td>• Nocturnal akinesia/tremor</td>
</tr>
<tr>
<td>• Anxiety</td>
<td>• RLS/PLMS</td>
</tr>
<tr>
<td>• Slowness of thought</td>
<td>-Sensory symptoms</td>
</tr>
<tr>
<td>• Psychosis</td>
<td>• Diminished sense of smell</td>
</tr>
<tr>
<td>Autonomic dysfunctions</td>
<td>• Pain</td>
</tr>
<tr>
<td>• Neurogenic bladder</td>
<td>• Numbness</td>
</tr>
<tr>
<td>• Erectile dysfunction</td>
<td>• Paresthesia</td>
</tr>
<tr>
<td>• Constipation</td>
<td></td>
</tr>
</tbody>
</table>

Fatigue
Atypical Parkinsonism

Corticobasal Degeneration (CBD)
Progressive Supranuclear Palsy (PSP)
Multiple System Atrophy (MSA)
Lewy Body Dementia (LBD)

These diseases share common features:

- Quicker progression
- Poor response to levodopa
- Early cognitive involvement (LBD, PSP)
- Early problems with gait and balance (PSP, MSA)

Atypical Parkinsonisms

<table>
<thead>
<tr>
<th>Corticobasal syndrome</th>
<th>Progressive supranuclear palsy</th>
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<tbody>
<tr>
<td>~2,000 in US</td>
<td>~20,000 in US</td>
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</tbody>
</table>

- 50% show clumps of tau
- 25% show tau and amyloid-beta
- 20% show alpha-synuclein
- 5% involve other proteins

- Muscle jerks
- Dystonia
- Cognitive impairment
- Apraxia

- Clumps of tau
- Tendency to fall backwards
- Restricted extraocular movements and saccades
- Mood and behavioral changes
- Speech and swallowing problems
### Atypical Parkinsonisms

<table>
<thead>
<tr>
<th>Multiple system atrophy</th>
<th>Lewy body dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>~80,000 in US</td>
<td>~15,000 in US</td>
</tr>
<tr>
<td>- Gait instability</td>
<td>- Cognitive impairment/dementia</td>
</tr>
<tr>
<td>- Dysarthria</td>
<td>- Hallucinations</td>
</tr>
<tr>
<td>- Autonomic dysfunction</td>
<td>- Mood/behavioral changes</td>
</tr>
<tr>
<td>‒ Orthostatic hypotension</td>
<td>- Fluctuations in alertness</td>
</tr>
<tr>
<td>‒ Urinary issues</td>
<td>- Hypersomnolence</td>
</tr>
<tr>
<td>‒ Constipation</td>
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<tr>
<td>‒ Sexual function</td>
<td></td>
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<tr>
<td>‒ Temperature regulation</td>
<td></td>
</tr>
<tr>
<td>‒ Sleep issues</td>
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### How to treat

- No neuroprotective therapies for Parkinson’s Disease or atypical parkinsonisms
- Levodopa usually first treatment for motor symptoms, but usually no robust or prolonged benefit in atypical parkinsonism
- Symptomatic management, assistive devices, PT, OT, social work, palliative
- Therapies against these proteins (alpha-synuclein, tau, amyloid-beta) are in clinical trial
Shake, rattle and roll: the hyperkinetic movement disorders

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Hypokinetic vs Hyperkinetic

• Bradykinesia
• Parkinsonian disorders

• Tremor
• Dystonia
• Tics
• Chorea
**Dystonia**

- **DEFINITION:** twisting repetitive movements or abnormal postures that arise from involuntary muscle contractions

- **Focal**
  - Neck
  - Eyes
  - Limb

- **Generalized**

**Dystonia classification**

**Classification on cause**

- **Primary**
  - Focal dystonia, Generalized childhood dystonias (DYT1, DYT6)

- **Dystonia plus syndromes**
  - Dopamine responsive dystonia
  - Rapid onset dystonia parkinsonism
  - Myoclonus dystonia
  - X-linked dystonia parkinsonism (DyT3)

- **Secondary dystonia**
  - Due to trauma, stroke, drugs
Focal dystonia

- Cervical dystonia
  - Torticollis
  - Laterocollis
  - Anterocollis
  - Retrocollis
- Blepharospasm
- Writer’s cramp
- Oromandibular dystonia

Geste antagoniste in dystonia

A PURPOSEFUL MOVEMENT THAT SUPPRESSES THE INVOLUNTARY DYSTONIC MOVEMENT
- Unique to dystonia
- Hand on side of face, touching back of head for torticollis
- Walking backwards or running may reduce leg dystonia
- Placing objects in mouth for orolingual dystonia
**Task specific dystonia**

- May be task specific
  - Throwing a ball
  - Writer’s cramp
  - Musician dystonia— Leon Fleisher pianist
  - Golfers’ “Yips” = jerking while putting

**Oppenheim dystonia**

- Inherited primary dystonia
  - 1/2000 Ashkenazi Jews
  - 1/20,000 in non-Jews
  - Autosomal dominant
  - TorsinA, GAG deletion
  - 30% penetrance
- 50% of patients affected by age 9, onset > 40 rare
- Most start in arm or leg, then spread to neck
  - Peculiar twisting of leg and foot when child walks forwards
- Eventual spread to generalized dystonia
Tics

- **Unvoluntary** production of movements or sounds
  - Motor and phonic
- Tics tend to change in repertoire, and wax and wane over time
- Premonitory sensation
  - Tingling, aching, itching, tension that takes place before the tic
- SUPPRESSIBLE
  - Patients describe increasing inner tension while suppress tics, followed by rebound of tics

Definite Tourette syndrome diagnostic criteria per the Tourette Syndrome Classification Study Group (TSCSG)

- Both multiple motor and one or more phonic tics present at some time during the illness, although not necessarily concurrently.
- Tics occur many times daily, nearly every day, or intermittently throughout a period of more than one year.
- Anatomic location, number, frequency, type, complexity, or severity of tics change over time
- Onset before age 21
- Involuntary movements and noises cannot be explained by other medical conditions.
- Tics witnessed by a reliable examiner directly or recorded by videotape.

Tremor

- Tremor is the most common movement disorder in outpatient practice
- INVOLUNTARY, RHYTHMIC OSCILLATION of a body part
  - RHYTHMIC, constant frequency
  - AXIS of tremor
  - Alternating contractions of reciprocally innervated/antagonist muscles
## Classification of tremors

- **Rest versus action**
  - Resting tremor in repose
  - Action tremor = all tremor manifestations of body parts that are not at rest
    - Kinetic occurs with movement
    - Postural tremor in antigravity posture
    - Task-specific (writing, golf tremor)
    - Isometric (fist squeeze, orthostatic tremor) = voluntary contraction of muscles NOT accompanied by change in position of body part
- **Frequency**
  - Parkinson 3 to 5 Hz
  - ET 5 to 10 Hz
  - Orthostatic tremor 12 to 18 Hz
  - Holmes, cerebellar tremor, <= 4Hz

## ESSENTIAL TREMOR

- Upper limbs in 95% of patients
- Head 34% patients
- Face/jaw 7% patients
- Voice 12%
- Tongue 30%
- Trunk 5%
- Lower limbs 30%
Essential Tremor

- Bimodal age of onset peaks in second and sixth decades
- Up to 5% of population
- Family history in about 50% cases
- LINGO1 gene sequence variation association
- SLC1A2 glial glutamate transporter gene polymorphisms

Rubral tremor

- Midbrain injury (stroke, trauma)
- Lesion of cerebello-thalamic projections: combined hit to superior cerebellar peduncle, substantia nigra, and red nucleus
- Damage to:
  - Outflow pathway from cerebellum to motor thalamus
  - Dopaminergic-thalamic system
- Tremor at rest, posture, and action
- SLOW <=4 Hz
- Ipsilateral dysmetria and dysdiadochokinesia
- Delay 1 to 24 months
Chorea

- Involuntary continual irregular and unsustained movements that flow randomly from one body part to another
- Motor impersistence
- Parakinesia: incorporate movement into voluntary action
- Lurching gait
- Irregular speech

Huntington Disease

- CHOREA
  - Starts with clumsiness/fidgetiness
  - Progresses to frank chorea
  - Chorea affects diaphragm, pharynx, larynx producing dysarthria and dysphagia
  - Motor impersistence
  - Later parkinsonism (akinetic rigid state)

- PSYCHIATRIC DZ
  - Depression, psychosis

- DEMENTIA
  - Executive dysfunction
  - Eventual profound dementia

- EYE MOVEMENTS
  - Slowed saccades (early sign)
  - Delay in volitional saccades
  - Impaired smooth pursuit
Huntington Disease

- Genetic basis is expansion of a CAG repeat encoding part of the protein huntingtin on CHR4
  - Autosomal dominant, full penetrance
  - Toxicity of mutant huntingtin protein
  - Normal 15-32 CAG repeats
  - > 38 repeats → HD
  - Higher number of repeats, the earlier onset (anticipation)
- Genetic testing commercially available
  - Always do genetic counseling and neuropsych eval first
- Prevalence in 4 to 8 per 100,000 in Europe, North America, lower in non-Europeans
- Atrophy of the striatum, especially caudate

Wilson disease

- Autosomal recessive
- Hepatic copper transport protein ATP7B
  - ATPase that binds copper and transports copper across cellular membranes using ATP
  - Over 300 different mutations, 1/90 people
- ATP7B mutation leads to
  - Decreased transport of copper from liver into bile → COPPER EXCESS
  - Impaired incorporation of copper into apocerulopalsmin, leads to diminished formation ceruloplasmin
    - Low ceruloplasmin used diagnostically, but not important clinically
- Copper accumulates in liver, spills into the blood, deposits in the brain
## Wilson disease

- Presents usually between age 10 and 25, but variable
  - Liver disease (18 to 84% of patients)
  - Neurologic symptoms (18 to 73%)
  - Psychiatric symptoms (10 to 100%)
- Children typically present with liver disease
  - Chronic active hepatitis
  - Asymptomatic liver enzyme elevations
  - Cirrhosis
  - Acute liver failure
- Neurologic disease: can present with many movement disorders
  - TEST ANYONE YOUNGER THAN 50 WITH MOVEMENT DISORDER FOR THIS

## Wilson disease: pathogenesis

- Copper accumulates in liver
  - Eventual liver damage from copper
- Copper leaks into the blood
  - Elevation in free serum copper levels
  - Note total serum levels may not be elevated due to low ceruloplasmin
- Copper deposits into the brain
  - Brain eventually atrophic
  - Putamen and caudate brown and shrunken
  - Advanced: spongy degeneration of subcortical white matter and cortex
### Wilson disease: clinical manifestations

- Dysarthria
- Dystonia
- Tremor
- Parkinsonism
- Ataxia
- Chorea
- Risus sardonicus: dystonia in facial muscles
- Seizures
- Hyperreflexia
- Kaiser Fleischer rings
  - Copper in cornea

### Video Wilson disease