Hypokinetic 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”

Classification of parkinsonism

Primary
• Parkinson’s disease
• Juvenile parkinsonism

Secondary
• Infectious
• Drugs
• Toxins
• Vascular
• Trauma
• Metabolic

Atypical parkinsonian syndromes
• Corticobasal degeneration (CBD)
• Progressive Supranuclear Palsy (PSP)
• Multiple System Atrophy (MSA)
• Lewy Body Dementia (LBD)

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 La Deau LM, Breitner MM. Lancet Neurol 2006
Kowal, SL, Doll, 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 ([123I]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

### UK Brain Bank criteria

#### Inclusion criteria
- Bradykinesia
- At least one of the following:
  - Muscular rigidity
  - 4-6Hz rest tremor
  - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

#### Supportive criteria
- Unilateral onset
- Persistent asymmetry affecting side of onset most
- Rest tremor present
- Progressive disorder
- Excellent response (70-100%) to levodopa
- Levodopa-induced chorea
- Levodopa response for 5 yrs or more
- Clinical course of 10 yrs or more

### 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

### 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

**Neuropsychiatric symptoms**
- Dementia
- Depression
- Anhedonia
- Apathy
- Anxiety
- Slowness of thought
- Psychosis

**Autonomic dysfunctions**
- Neurogenic bladder
- Erectile dysfunction

**Fatigue**
- Sleep disturbances
  - REM sleep disturbances
  - Sleep fragmentation
  - Excessive daytime sleepiness
  - Nocturnal akinesia/tremor
  - RLS/PLMS
- Sensory symptoms
  - Diminished sense of smell
  - Pain
  - Numbness
  - Paresthesia

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**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)

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**Atypical Parkinsonisms**

- Corticobasal syndrome ~2,000 in US
  - 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

- Progressive supranuclear palsy ~20,000 in US
  - Clumps of tau
  - Tendency to fall backwards
  - Restricted extraocular movements and saccades
  - Mood and behavioral changes
  - Speech and swallowing problems

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## Atypical Parkinsonisms

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

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## Shake, rattle and roll: the hyperkinetic movement disorders

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## Hypokinet 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 (DysT3)
- 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 &lt;= 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
  - Slow 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 apoceruloplasmin, 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: 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