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"**

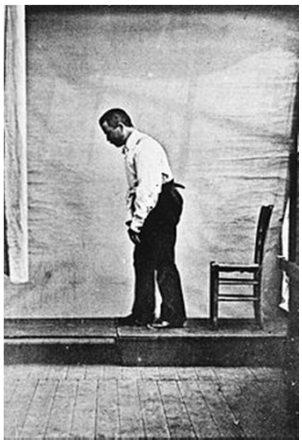


Photo by Arthur Londe from *Nouvelle Iconographie de la Salpètrière*, vol. 5., p.226

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)**

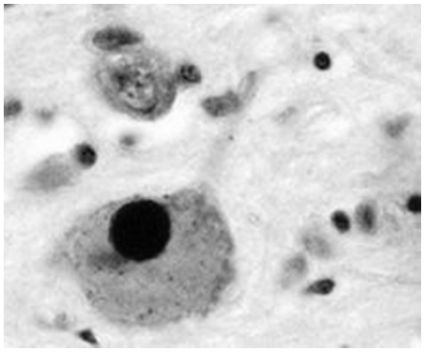
Parkinson's Disease

- **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 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

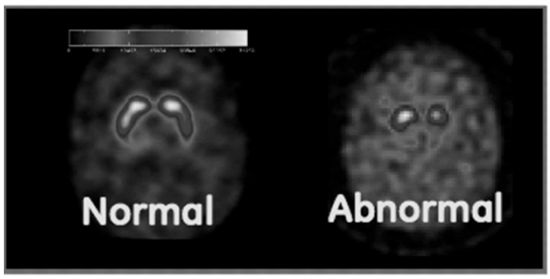


Diagnostic testing

- 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
$^{[123I]}$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

Hughes AJ et al. JNNP 1992; 55: 181-184.

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 tasks
- In 75% of pts is first motor manifestation
- Usually beings unilaterally
- Can occur intermittently and vary in intensity

Rigidity

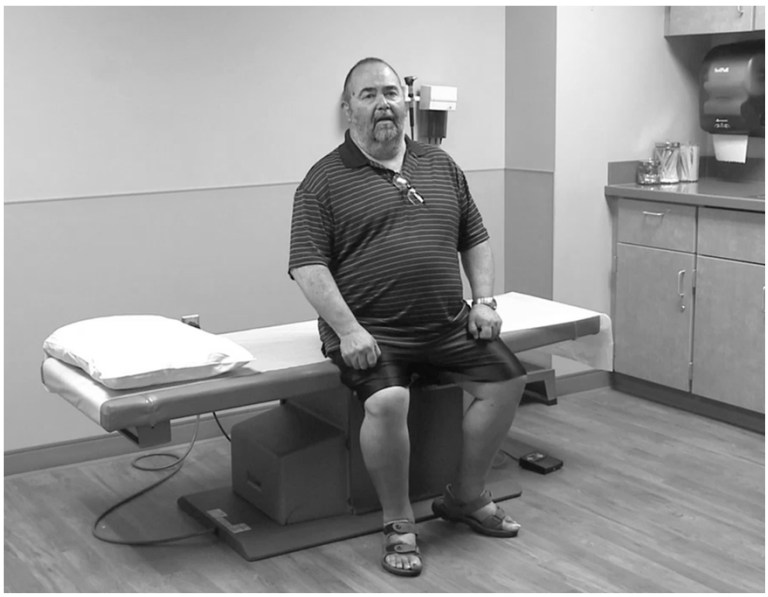
- Increased resistance to passive movement of limb segment

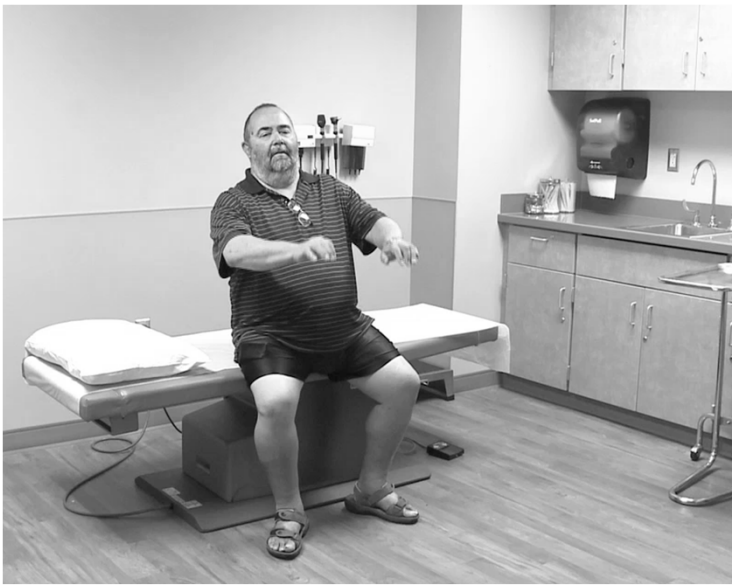
Bradykinesia

- 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**





Motor symptoms

Non-motor symptoms

Langston, JW. Ann Neurol 2006

Non-motor features

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

Autonomic dysfunctions
- Neurogenic bladder
- Erectile dysfunction
- Constipation

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

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

Corticobasal syndrome

~2,000 in US

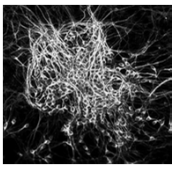
- **50% show clumps of tau**
- **25% show tau and amyloid-beta**
- **20% show alpha-synuclein**
- **5% involve other proteins**

- **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**

Atypical Parkinsonisms

Multiple system atrophy

~80,000 in US

- **Gait instability**
- **Dysarthria**
- **Autonomic dysfunction**
  - **Orthostatic hypotension**
  - **Urinary issues**
  - **Constipation**
  - **Sexual function**
  - **Temperature regulation**
  - **Sleep issues**

Lewy body dementia

~15,000 in US

- **Cognitive impairment/dementia**
- **Hallucinations**
- **Mood/behavioral changes**
- **Fluctuations in alertness**
- **Hypersomnolence**

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

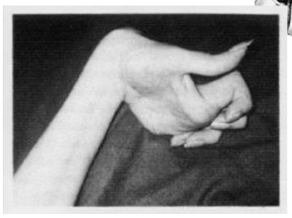
- **DEFINITION: twisting repetitive movements or abnormal postures that arise from involuntary muscle contractions**

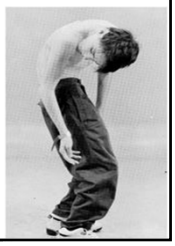
- **Focal**
  - **Neck**
  - **Eyes**
  - **Limb**
- **Generalized**

Dystonia classification

<u>Classification on cause</u>

- **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.

Tourette syndrome classification study group. Definitions and classifications of tic disorders. Arch Neurol. 1993;50:1013-1016.

Video Tourette

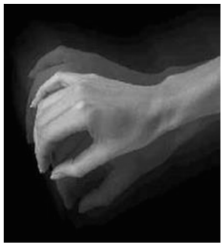
Tremor

- **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**

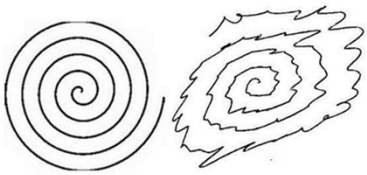
Classification of tremors

- **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



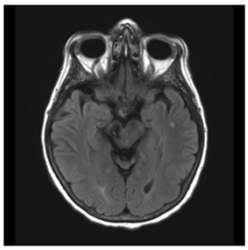
- **Upper limbs in 95% of patients**
- **Head 34% patients**
- **Face/jaw 7% patients**
- **Voice 12%**
- **Tongue 30%**
- **Trunk 5%**
- **Lower limbs 30%**



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

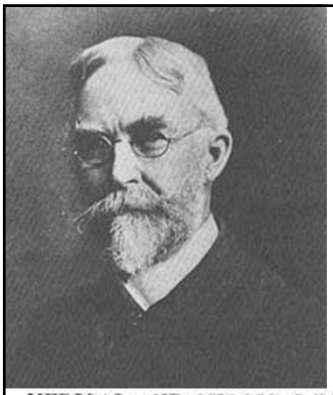
Rubral tremor



- 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



MEDICAL AND SURGICAL REPORTER.

No. 769.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

By George Huntington, M. D.,

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the dancing propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic spasm affecting the voluntary muscles. There is no loss of

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

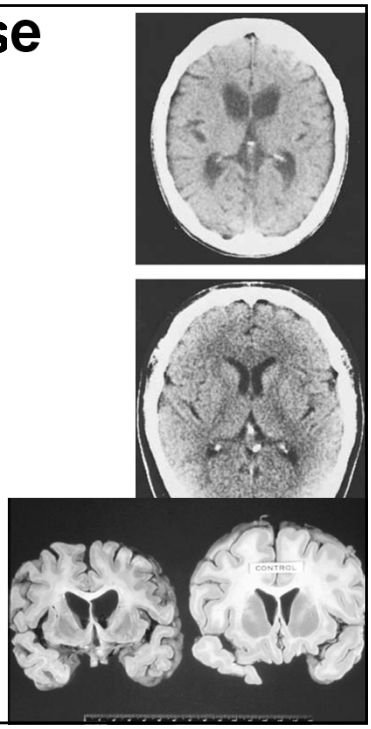
If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of them would be impossible. Sometimes the muscles of the lower extremities are not af-

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

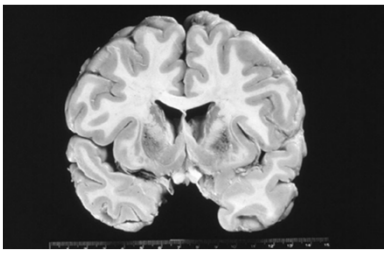
- Autosomal recessive
- Hepatic copper transport protein ATP7B
  - ATPase that binds copper and transports copper across cellular membranes using ATP
  - Over 300 different mutations, 1/90 people
- ATP7B mutation leads to
  - Decreased transport of copper from liver into bile→ COPPER EXCESS
  - Impaired 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

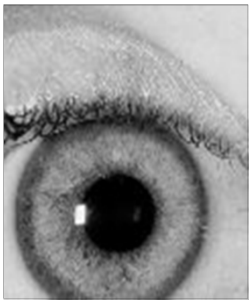
- Presents usually between age 10 and 25, but variable
  - Liver disease (18 to 84% of patients)
  - Neurologic symptoms (18 to 73%)
  - Psychiatric symptoms (10 to 100%)
- Children typically present with liver disease
  - Chronic active hepatitis
  - Asymptomatic liver enzyme elevations
  - Cirrhosis
  - 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