



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Movement Disorders

Barbara Kelly Changizi, MD

Director of Clinical Operations

Movement Disorders Division, Department of Neurology

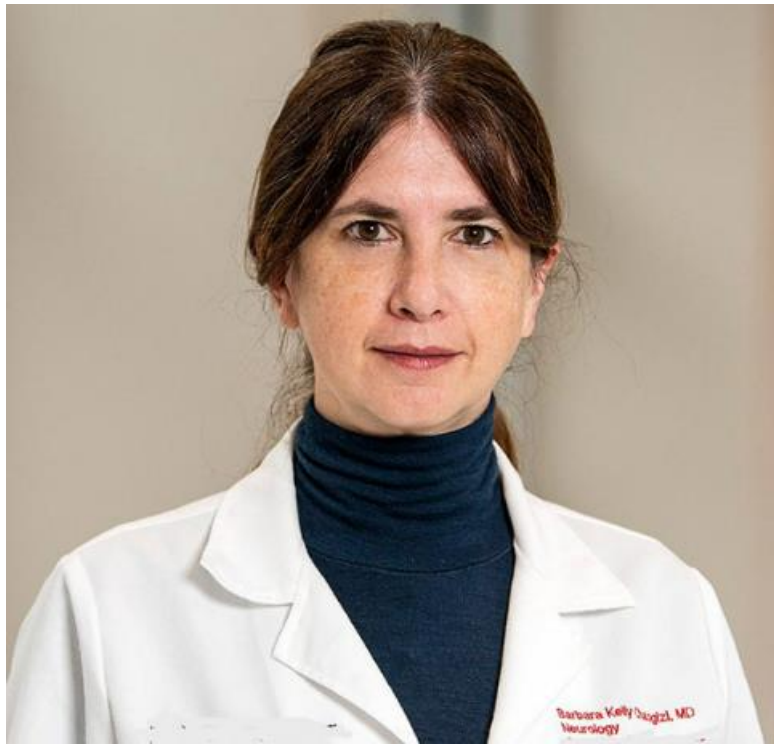
Brigham and Women's Hospital

Instructor of Neurology

Harvard Medical School



Barbara Kelly Changizi, MD



- Medicine Residency @ University of California Los Angeles
- Instructor of Neurology@ HMS
- Director of Clinical Operations, Movement Disorders Division@ BWH
- Clinical focus: Movement Disorders including deep brain stimulation (DBS), parkinsonian syndromes



DISCLOSURES

- I have nothing to disclose.



Objectives

- Differentiate hyperkinetic versus hypokinetic movement disorders
- Characterize the phenomenology of movement and correctly define it
- Use phenomenology combined with clinical history to construct a differential diagnosis
- Order imaging and laboratory testing as appropriate
- Construct treatment plan



Movements disorders are neurological disorders that originate from the basal ganglia or cerebellum. They affect the quality and abundance of movement.

Hyperkinetic

- Dystonia
- Tremor
- Chorea
- Tics
- Myoclonus



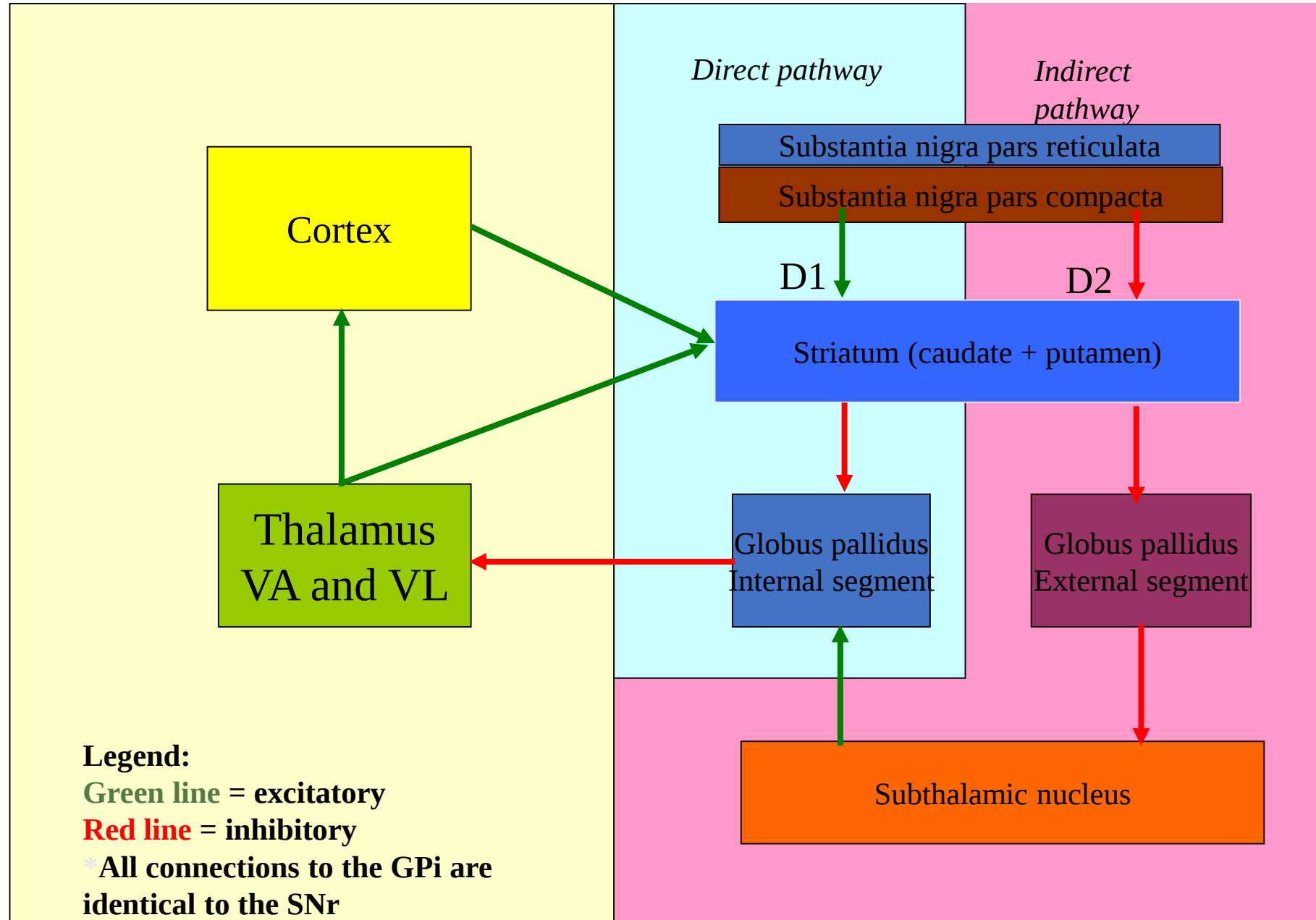
Hypokinetic

- Parkinsonism



Movement disorders original from problems in the basal ganglia.

The basal ganglia have direct and indirect pathways, which promote or inhibit movement



Hypokinetic disorders



Hypokinetic movement disorders— parkinsonism

- Most common is Parkinson disease (PD)
 - Second most prevalent neurodegenerative disease after Alzheimer's (Wirdefeldt 2011))
 - Population prevalence of PD increases from about 1% at age 60 to 4% at age 80 (Hamza 2011)
- Definition of parkinsonism: bradykinesia with EITHER rest tremor or rigidity
- Parkinsonian syndromes—disorders which cause parkinsonism but atypical presentation, more severe course, and additional early signs
 - Multiple system atrophy (MSA)
 - Progressive supranuclear palsy (PSP)
 - Cortical basal degeneration (CBD)
 - Dementia with Lewy Bodies (DLB) (we will not discuss here)



Diagnosis of Parkinson disease is made clinically

- Movement Disorders Society Diagnostic Criteria (2015)
 - Bradykinesia with EITHER rest tremor or rigidity, or both
 - Note that this differs from the UK Brain Bank Criteria of 2008 in which you must have bradykinesia with EITHER rest tremor, rigidity, *or postural instability*
- Bradykinesia (slowness of movements)
 - Soft voice, shuffling gait, masked face, decreased arm swing, slowed movements during rapid movement testing
- Tremor
 - Limb tremor 4-6 Hz, pill rolling, resting tremor, typically asymmetrical
 - May see chin or tongue tremor
- Rigidity: increased resistance to passive movement

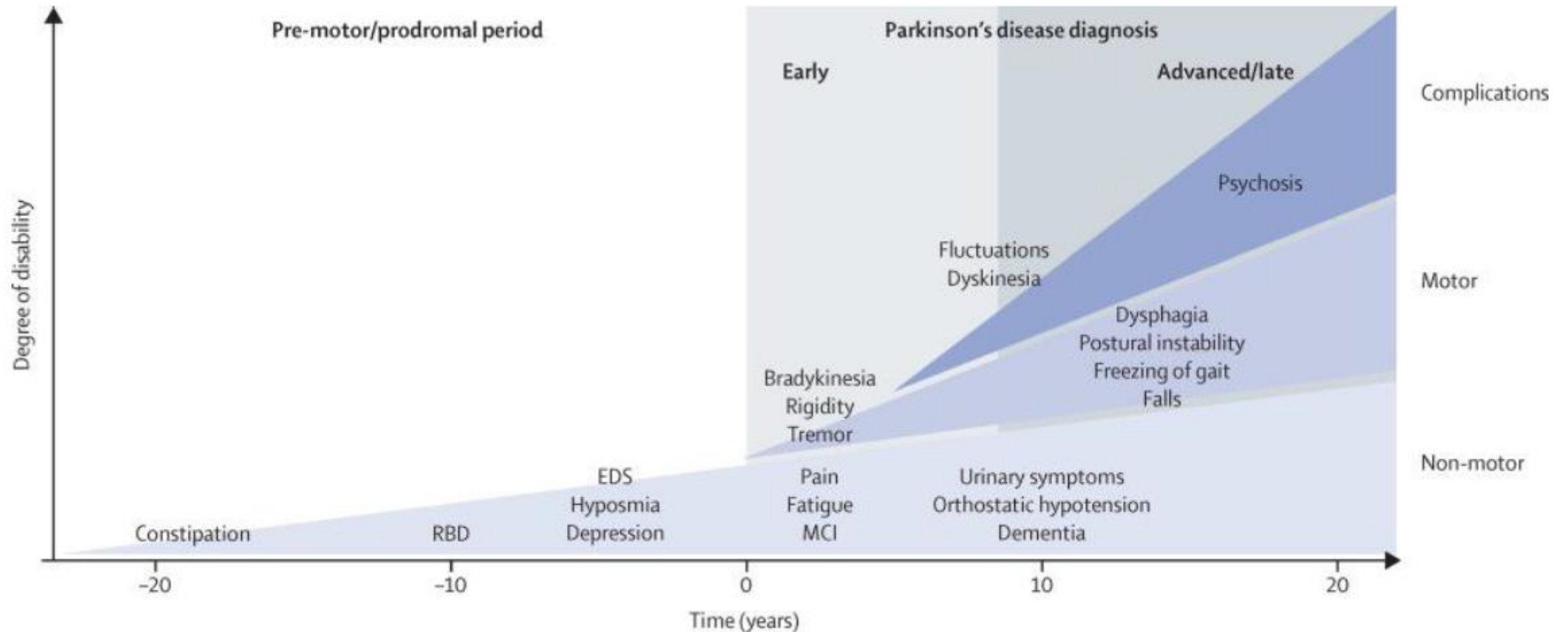


Video

- Bradykinesia bilaterally with rapid alternating movements
- Resting tremor in the right leg and arm
- Stooped posture
“Camptocormia”
- Shuffling gait
- Decreased facial expression
- Hypophonia

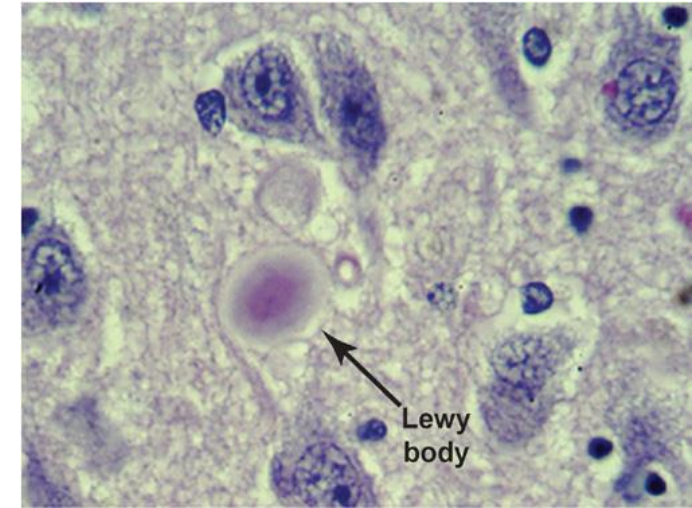


Disease course of Parkinson disease



Pathogenesis of PD

- Major function of basal ganglia circuitry is to control abundance and initiation of movement
- In PD, there is loss of dopaminergic neurons in the substantia nigra pars compacta
 - By the time PD motor features appear, 60% of neurons in the SNpc already lost (Hornykiewicz, 2006)
- Indirect pathway becomes overactive, and result is lack of movement, or bradykinesia
- Pathology shows atrophy of dopaminergic cells in the substantia nigra and alpha synuclein in Lewy bodies and neurites
- Cause of neurodegeneration remains unknown (inflammation, oxidative stress, protein aggregation, mitochondrial dysfunction, lysosomal dysfunction)



Ancillary diagnostic tests

- MRI brain is normal in patients with PD; we order this to exclude secondary parkinsonism (lesion to basal ganglia, NPH)
- DATscan (Dopamine transporter SPECT)
 - Uses ^{123}I -FP-CIT Single photon emission computed tomography (SPECT) imaging
 - Detects loss of dopaminergic terminals in the caudate and putamen
 - Detects neurodegeneration, is normal in essential tremor, vascular parkinsonism, neuroleptic induced parkinsonism)

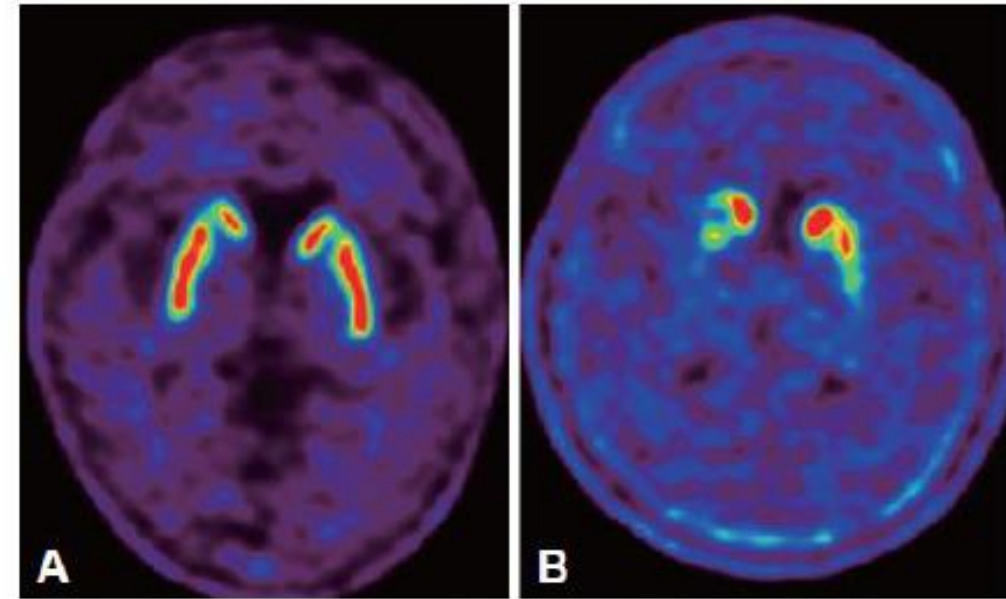


Fig. 2. ^{123}I -FP-CIT PET imaging in two DIP patients. DAT uptake was normal and symmetric in the bilateral striatum in a pure DIP patient (A), whereas it decreased severely in the right striatum in a patient who was diagnosed with PD unmasked by DRBAs (B). DAT: dopamine transporter, DIP: drug-induced parkinsonism, DRBA: dopamine receptor blocking agents, PD: Parkinson's disease.

Shin HW(1), Chung SJ. Drug-induced parkinsonism. J Clin Neurol. 2012 Mar;8(1):15-21.



Ancillary test (cardiac MIBG scintigraphy)

- Evaluates cardiac sympathetic denervation
- Ligand is metaiodobenzylguanidine (MIBG, iobenguane I-123)
- MIBG is taken up and stored in presynaptic vesicles similar to norepinephrine, then released into the synaptic cleft
- If there is postganglionic cardiac sympathetic denervation, there is decreased uptake of MIBG in the heart
- This is a supportive criteria for PD according to Movement Disorders Society

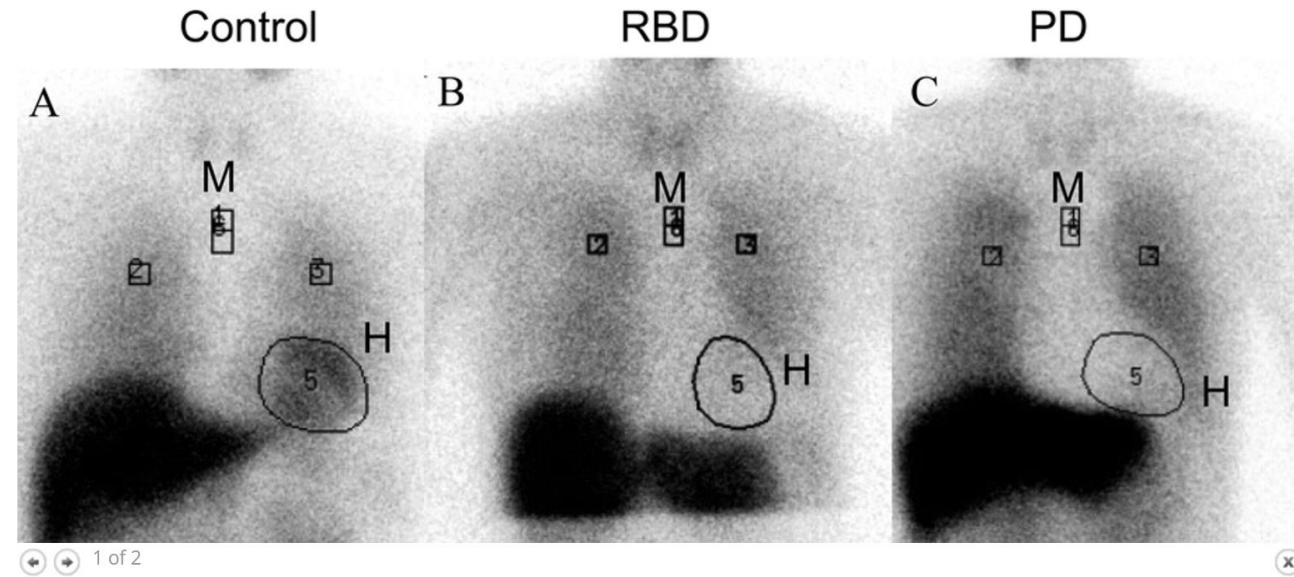


Figure 1. Planar cardiac delayed ^{123}I -metaiodobenzylguanidine (MIBG) imaging in representative control (A) and in patients with idiopathic RBD (B) and PD (C). Regions of interest regarding MIBG uptake in the heart (irregularly shaped region labeled with H) and MIBG uptake in the mediastinum (rectangular region indicated by M) are shown in the figure. Note the markedly reduced MIBG uptake in the patients with RBD and PD. RBD = REM behavior disorder; PD = Parkinson disease.

(Miyamoto ,2006)



Ancillary tests—skin biopsy

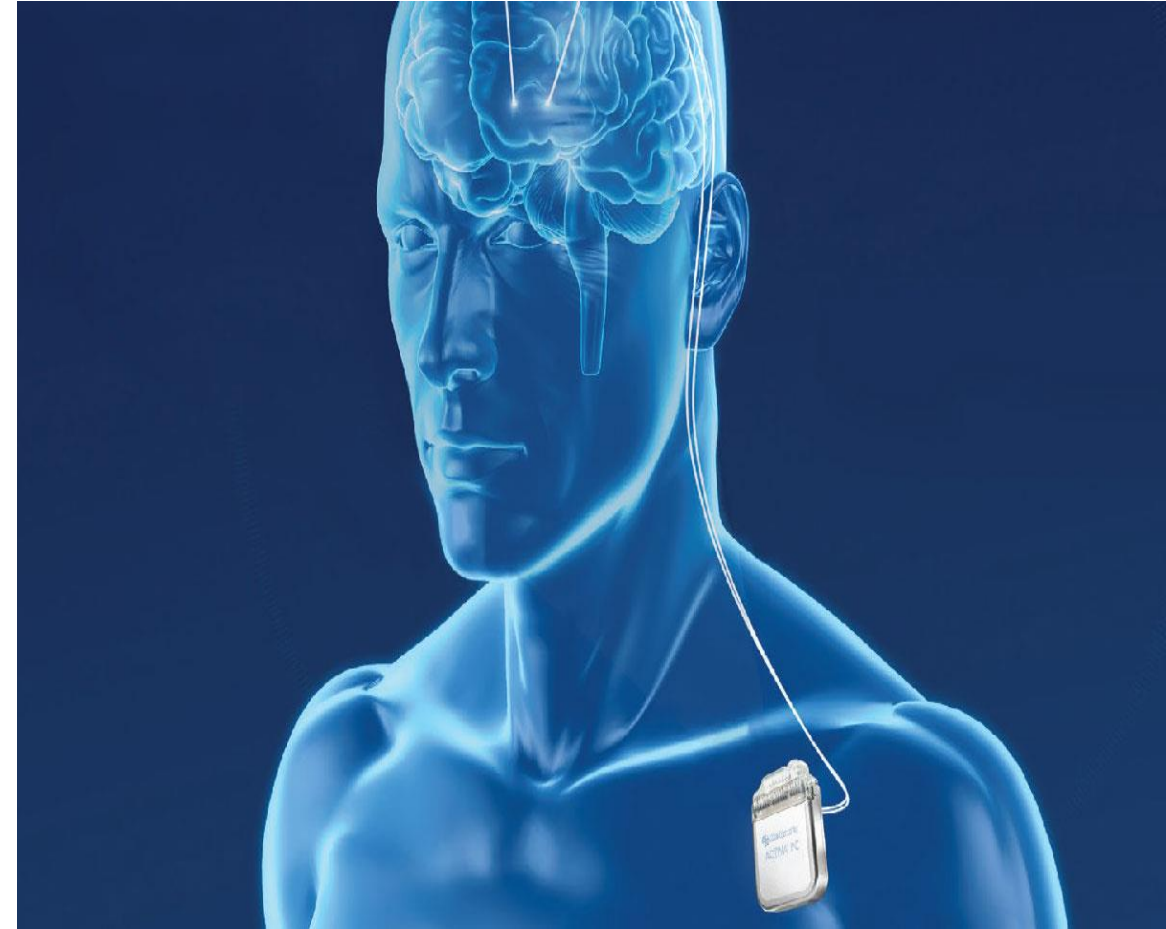
- Syn-One test detects abnormally phosphorylated alpha-synuclein (p-syn) in cutaneous nerves of the skin
 - Alpha synuclein is hallmark of PD
 - P-syn folds incorrectly and is problematic in neuron
- Abnormal p-syn appears early in synucleinopathies
 - Parkinson disease
 - Dementia with Lewy bodies
 - Multiple system atrophy
 - Pure autonomic failure
- Skin has nerves to regulate blood vessels, sweat glands, sensation
- Syn-One Test detects p-syn in patients with clinically confirmed synucleinopathy with 96% sensitivity and 97% specificity (Synuclein-One Study, 2023)
- (Gibbons et al, 2020) report 95%v sensitivity and specificity



Medications	Mechanism	When to use it	Side effects
Carbidopa/levodopa	Levodopa is converted to dopamine within the brain	Most efficacious medicine, start with this in older patients	Nausea, orthostatic hypotension, dyskinesia, hallucinations, fatigue
Pramipexole, ropinirole, rotigotine, apomorphine	Dopamine agonist (D2)	Early monotherapy in younger patients, adjunct to levodopa, rotigotine comes in a patch, apomorphine is subcutaneous injection or sublingual films	As above as also dopaminergic PLUS impulse control disorders (gambling, shopping, etc), sleep attacks.
Selegiline, rasagiline, safinamide	Monoamine oxidase inhibitor type B, stops metabolism dopamine	Early monotherapy, adjunct therapy	Selegiline is metabolized to a stimulant (useful if fatigued), Serotonin syndrome risk Tyramine crisis is myth
Entacapone, opicapone	COMT inhibitor (stops metabolism dopamine)	Adjunct to levodopa	May exacerbate side effects of Ldopa, particularly dyskinesia
Istradefyline	Selective adenosine A2A receptor antagonist	Adjunct to levodopa in patients with motor fluctuations	Dyskinesia
Amantadine (IR and ER)	Dopamine reuptake, NMDA receptor antagonist, anticholinergic	Anticholinergic effects help tremor, mild dopaminergic effect, NMDA effects help dyskinesia	Hallucinations, anticholinergic, rare corneal edema
Trihexyphenidyl	Anticholinergic	Tremor	Dry eyes, dry mouth, constipation, cognitive impairment, urinary retention Exposure may increase risk of dementia (Coupland 2019)

Deep brain stimulation (DBS)

- DBS is done when patients have moderately advanced PD with motor fluctuations
 - Cognitive impairment is a contraindication to this surgery
- A lead is implanted into a specific target within the brain (globus pallidus, subthalamic nucleus) to allow electric current to stimulate the brain
- Electrical signal suppresses abnormal firing patterns in the brain (beta band) associated with motor symptoms of parkinsonism
- DBS can dramatically improve motor fluctuations and medication requirement
- (Image from Medtronic)

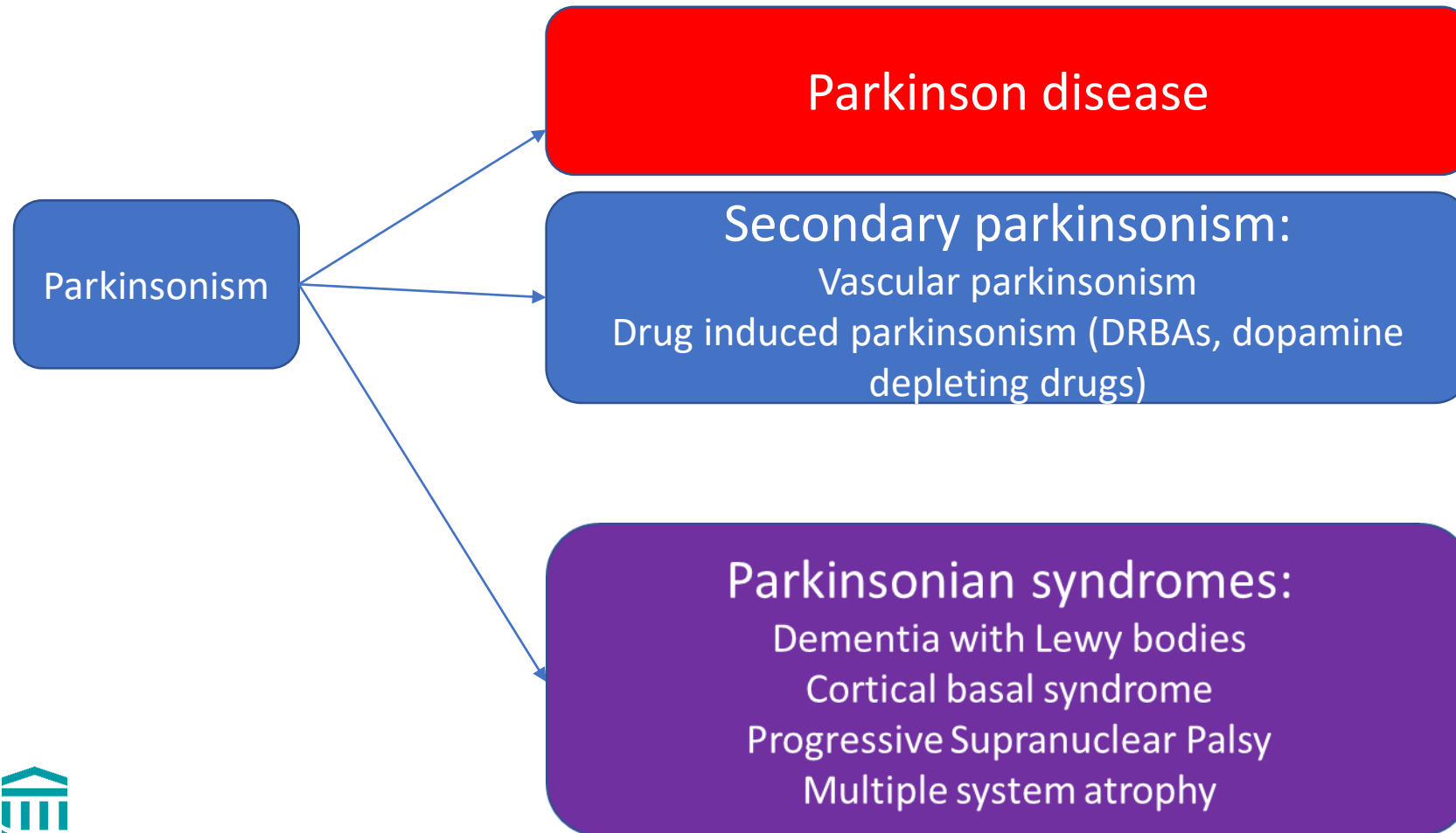


Treatment of Parkinson disease non-motor symptoms

Dementia	Only rivastigmine is FDA approved for PD dementia
Depression	SSRIs, TCAs
Hallucinations, delusions	Quetiapine, pimavanserin, clozapine
Constipation	Miralax, lubiprostone
Orthostatic hypotension	Midodrine (alpha2 receptor agonist and vasoconstrictor), fludrocortisone (mineral corticoid that decreases sodium loss in urine), droxidopa (norepinephrine prodrug), pyridostigmine (peripheral AchEsterase inhibitor, may enhance nicotinic ganglionic transmission in the sympathetic ganglia to increase diastolic BP, increases total peripheral resistance)
Drooling	Sublingual ipratropium, glycopyrrolate, botulinum toxin injections to salivary glands, atropine eye drops SL
Incontinence	Mirabegron, oxybutynin, trospium
Active dreaming	Melatonin, clonazepam at bedtime



Differential diagnosis of parkinsonism



Consider parkinsonian syndromes in patients with parkinsonian features who are not responsive to levodopa, rapid course. Each of these disorders eventually develops signs and symptoms that distinguish it from PD, but may not be present at disease onset



Progressive supranuclear palsy (PSP)

- Parkinsonism that does NOT respond to Ldopa
 - Rigidity which is axial > limb
 - Neck may be extended (retrocollis)
 - No resting tremor, but may see postural tremor
- Early postural instability with falls
- Unusual facial expression, labeled dystonia, with deep nasolabial folds and furrowed brow
- Supranuclear ophthalmoplegia
 - Failure of voluntary vertical gaze (downgaze first)
 - Later paralysis of horizontal gaze
 - Oculocephalic and oculovestibular reflexes preserved
- Pseudobulbar palsy
 - Facial weakness, dysarthria, dysphagia—anarthric early
- Early cognitive impairment
- Pathological hallmark is microtubule-associated protein tau aggregates
- Prevalence 5 to 7 per 100,000, incidence increases with age, average age onset 65 (Schrag 1999)

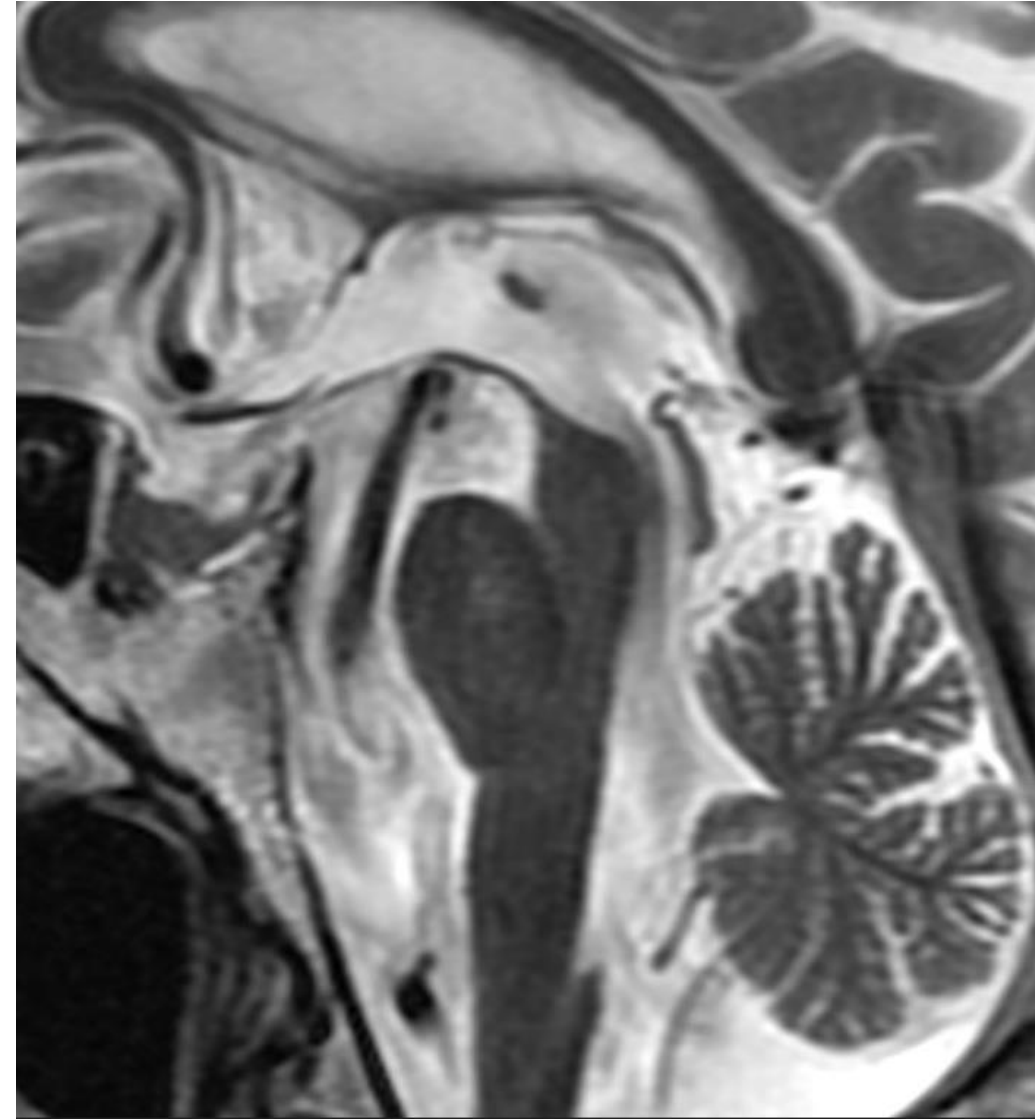


PSP MRI brain

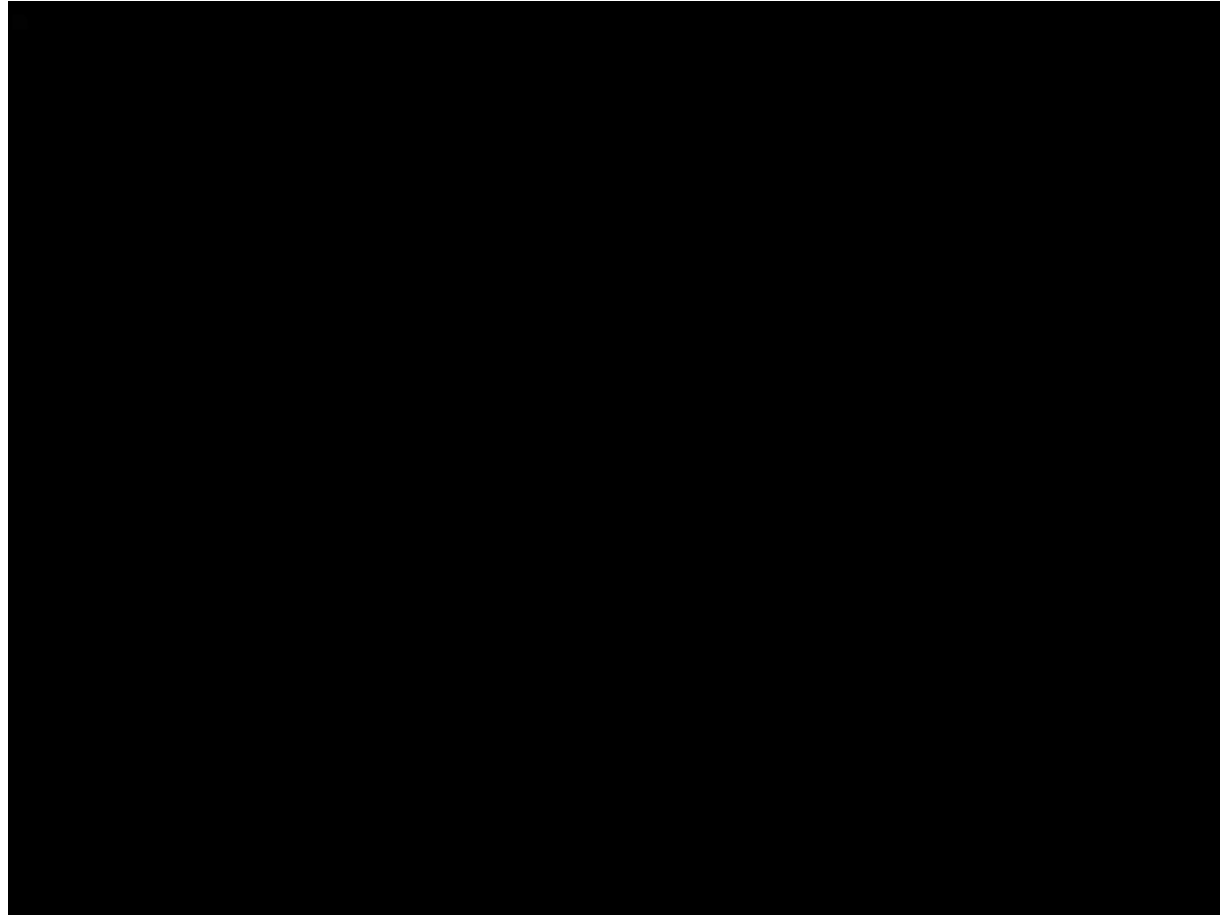
Midbrain atrophy (Hummingbird or penguin signs on midsagittal images, or mickey mouse or morning glory signs on axial images)

There are also various ratios to demonstrate disproportionate midbrain atrophy

Case courtesy of Prashant Gupta, Radiopaedia.org. From the case rID: 18863



Video of PSP



Multiple system atrophy (MSA)

- Presents with parkinsonism, dysautonomia, and cerebellar signs in various combinations
 - MSA C versus MSA P
- Parkinsonism: bradykinesia and rigidity that do not respond to Ldopa, or has fast exhaustion of benefit with very early motor fluctuations, rapid progression
 - Axial dystonia with anterocollis (dropped head)
- Autonomic disorder
 - Orthostatic hypotension, supine hypertension
 - Anhidrosis
 - Impotence
 - Urinary dysfunction
 - Constipation
- Pyramidal signs: Babinski signs, brisk lower extremity reflexes, striatal toe
- Cerebellar issues: ataxia, dysmetria, nystagmus
- Prodromal symptoms: Rem sleep behavior disorder and dysautonomia, INTACT SMELL

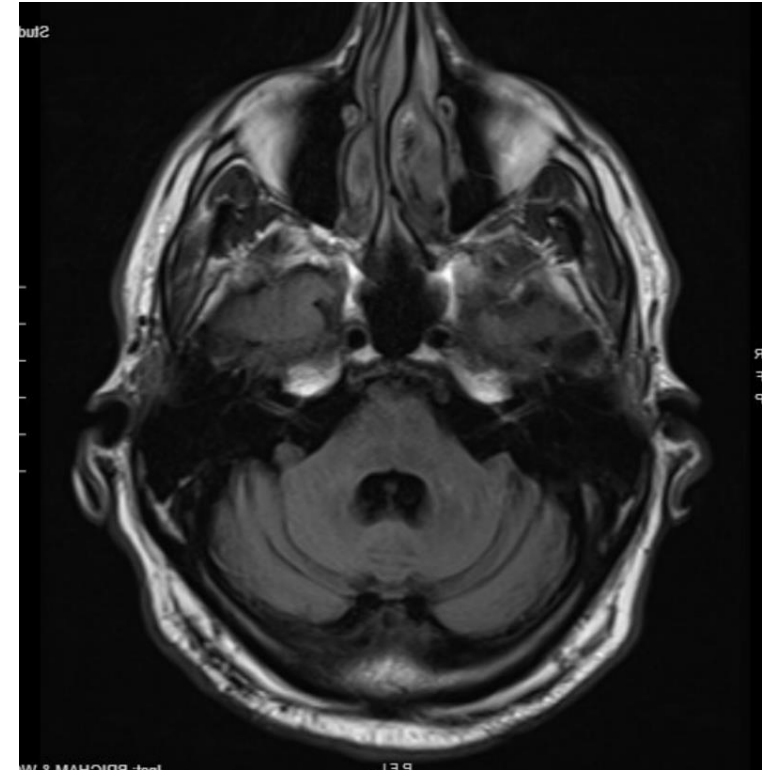


MSA Pathology and Imaging

- Alpha synuclein positive cytoplasmic inclusions in the oligodendrocytes
“Glial cytoplasmic inclusions”
- Lewy body inclusions in the cytoplasm of neurons
- Imaging: hot cross buns
- Pontine, cerebellar atrophy
- From Msa Radiopaedia.org



Video MSA-C



Skin biopsy positive for synuclein

Corticobasal degeneration (CBD)

- Rare, prevalence 5 to 7/100,000 (Pantelyat 2022)
- Probable CBD is asymmetric presentation and
 - at least 2 of limb rigidity or akinesia, limb dystonia, or limb myoclonus PLUS
 - At least 2 of orobuccal or limb apraxia, cortical sensory deficit, and alien limb phenomenon
- Parkinsonism Poorly responsive to levodopa
- Cortical signs
 - Limb apraxia = inability to make voluntary movement despite normal strength and sensation
 - Alien limb: reflects parietal lobe pathology, lack of awareness of movement on the patients' part
 - Cortical myoclonus
 - Cortical sensory loss of same limb = agraphesthesia, asteroagnosia
 - Aphasia
- Pathology: Tauopathy
 - Hyperphosphorylated 4 repeat tau inclusions in astrocytes, glia, neurons
 - CBD has astrocytic plaques, while PSP has tufted astrocytes
 - Globular tangles called "corticobasal bodies"



Videos of CBD



Hyperkinetic disorders



Tremor

- Tremor is an involuntary, rhythmic, oscillatory movement
- Rhythmic—describe the frequency
 - Examples—frequency can give you some clues:
 - Parkinson 4 to 6 Hz
 - Essential tremor 6 to 12 Hz
 - Orthostatic tremor 12 to 18 Hz
 - Midbrain tremor ≤ 4 Hz
 - Physiologic tremor: 10 to 12 Hz
- Oscillatory (rotating around a central plane)—LOOK FOR AN AXIS



Classification of tremors

Resting tremor

- Occurs in a body part that is fully supported, relaxed, not voluntarily activated
- Pearls
 - Observe patient reciting months or serial 7s, or when walking dangling hands

Action tremor

Occurs with voluntary muscle contraction

- Kinetic occurs with voluntary movement
 - Simple kinetic: frequency and amplitude constant through movement
 - Intention tremor (sometimes called cerebellar outflow): crescendo increase as approach target
 - Task specific (writing tremor)
- Postural tremor occurs in specific posture, e.g. in antigravity posture or standing
- Isometric = tremor during muscle contraction against stationary object (no change in position of limb)
 - Making fist
 - Squeezing object



Physiologic tremor

- Everyone shakes—we have a physiologic oscillation firing in our brains
- Low amplitude, 10-12 hz tremor that is typically so low amplitude this is not detectable
- Fatigue and sympathetic activity exacerbate this
 - Drugs that increase sympathetic activity
 - Withdrawal from CNS depression (alcohol withdrawal, opioid withdrawal)
 - Thyrotoxicosis
 - Pheochromocytoma
 - Anxiety



Drugs that cause tremor

Mechanism is Increase adrenergic activity

- Beta adrenergic agonists
 - Terbutaline
- Epinephrine
- Amphetamines
- SSRIs
- TCAs
- Nicotine
- Theophylline
- Caffeine

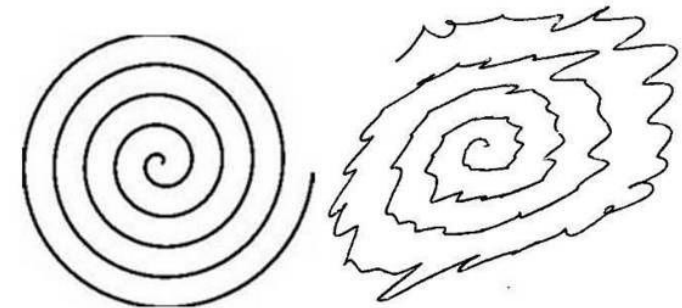
• Mechanism unclear

- Lithium
- Steroids
- Valproic acid
- Mercury
- Arsenic
- Lead
- Bromides
- Immunosuppressants
Tacrolimus, sirolimus
(toxicity causes tremor in 35 to 55% patients)



Essential tremor

- Movement Disorders Society consensus statement: essential tremor is defined as an isolated tremor syndrome of bilateral upper limb action tremor of at least a 3-year duration, with or without a tremor in other locations, and absence of other neurological signs such as dystonia, ataxia or parkinsonism.
 - TREMOR WHEN USING YOUR HANDS TO WRITE, USE UTENSILS, HOLD A CUP, DO HYGIENE
- May be improved with alcohol
- Tremor typically symmetrical
 - See asymmetrical hand and leg tremor, think PD
- 6-12 Hz frequency
- Tremor may spread to the head, voice, tongue, jaw, and legs
- Bimodal distribution of age, peak onset in 2nd and 6th decades of life
- Common: >5% people at least 65 years old have ET (Louis 2010)

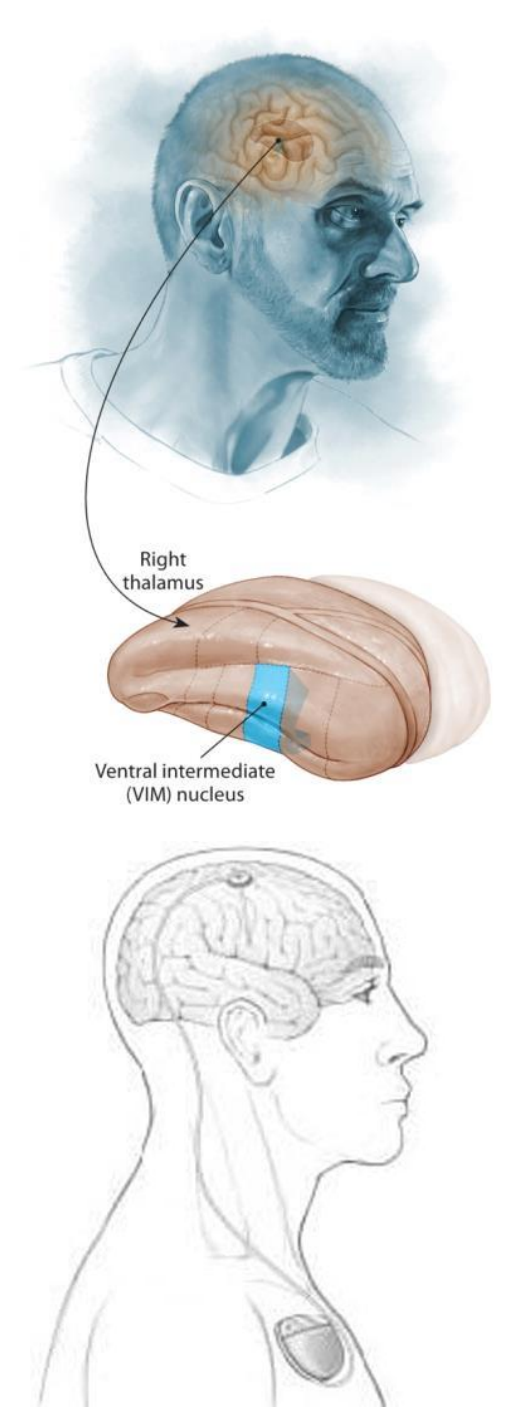


Treatment of essential tremor

- Propranolol: 1st line therapy, reduces tremor by about 50% to 70% in 50% of patients (Ondo 2020)
 - SE: fatigue, erectile dysfunction, bradycardia
- Primidone: first line therapy, SE confusion, ataxia, nausea

Above have synergistic benefit

- Gabapentin: 2nd line therapy
- Topiramate: 2nd line therapy
- Botulinum toxin for head tremor
- Deep brain stimulation
- High frequency ultrasound ablation procedure



Video



Dystonia

“Sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.”

- Taken from a consensus statement in Albanese A et al, Mov Disord 2013



Dystonia clinical features

- May be task specific
 - Throwing a ball
 - Writer's cramp
 - Musician dystonia
- May start with action but over time persist, spread to other body parts
- Sensory tricks (gestes antagonists)
 - Simple movements directed at the body region affected by the dystonia, but not in forceful opposition to the phenomenology of the dystonia
 - (Albanese et al, Mov Disord 2013)
 - Unique to dystonia
 - Examples
 - Hand on side of face, touching back of head for torticollis
 - Lying down to reduce truncal dystonia
 - Walking backwards or running may reduce leg dystonia
 - Placing objects in mouth for orolingual dystonia



Dystonia classified by etiology

- Nervous system pathology
 - Degenerative
 - Parkinson disease
 - Static lesions (nonprogressive developmental anomalies or acquired lesions)
- Acquired
 - Perinatal brain injury
 - Infection
 - Drugs
 - Toxic
 - Vascular
 - Neoplastic
 - Brain injury
- Inherited or acquired
 - Autosomal dominant: DYT1, DYT5, GYT5, DYT11, DYT12, DRPLA, HD, NBIA3
 - Autosomal recessive: NBIA1 or PKAN, Wilson disease, juvenile PD (park2), PLAN, metabolic disorders
 - Mitochondrial: Leigh syndrome, Leber optic atrophy and dystonia
- Idiopathic



Focal dystonia

- Most common form with adult-onset dystonia
- Cervical dystonia
 - Torticollis
 - Laterocollis
 - Anterocollis
 - Retrocollis
- Blepharospasm
- Writer's cramp
- Oromandibular dystonia



Dystonia—DYT-TOR1A (formerly DYT1)

- Mutation of loss of 3 base pairs in the torsin1A gene, encodes torsin A (ATP binding protein)
- Autosomal dominant with reduced penetrance
- Most common genetic dystonia
- Childhood with limb onset, progresses to generalized dystonia
- More common in Ashkenazi Jewish ancestry
- Onset > 40 rare



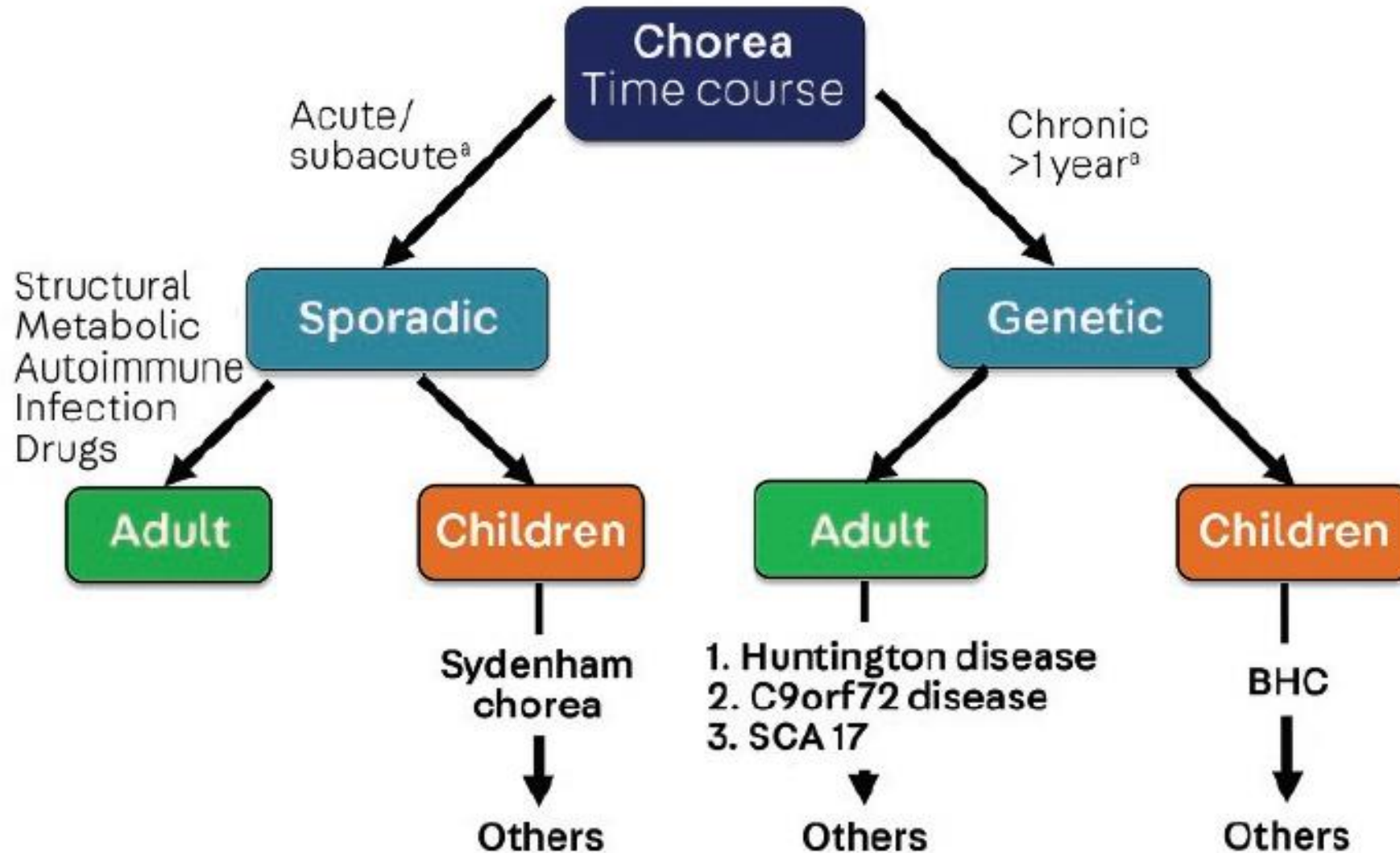
Treatments for dystonia	Indication	Side effects
Trihexyphenidyl (anticholinergic)	Any dystonia	Anticholinergic: impaired mentation, dry eyes, dry mouth, constipation, urinary retention. Concern that use may increase risk of dementia over time.
Carbidopa/levodopa	Consider a trial in childhood or young adult-onset dystonia in case this is dopamine responsive dystonia.	Nausea, lightheadedness, fatigue, nightmares, hallucinations
Dopamine depleting drugs (VMAT2 antagonists—prevents loading of dopamine into presynaptic vesicles	Tardive dystonia, oromandibular dystonia	Parkinsonism, akathisia, depression
Baclofen (antispasticity, GABA-B agonist, thought to block release of excitatory neurotransmitters from pre-synaptic neurons)	Any dystonia	Impaired mentation, fatigue, nausea, weakness, screen for withdrawal
Benzodiazepines (GABAergic)	Any dystonia	Potentially addictive, impaired mentation, drowsiness, impaired coordination, withdrawal
Botulinum toxin injections (toxin produced by c. botulinum results in local paralysis and alters sensory feedback)	Focal dystonia	Requires repeat injections every 3 months, high doses can cause excessive weakness (resolves over time)
Deep brain stimulation to the globus pallidus		

Chorea

- Characterized by the involuntary, random and flowing involuntary movements, appear dancelike
- Movements flow from one body part to another
- Parakinesia: patients blend voluntary movements with involuntary chorea
- Motor impersistence: inability to perform sustained motor activities
 - Tongue protrusion—tongue retracts back into the mouth after several seconds
 - Handgrip waxes and wanes “Milkmaid’s grip”
- Ballism: a variant of chorea characterized by large-amplitude flinging movements involving proximal extremities (diagnosis and treatment are same as for chorea)
 - Hemiballismus: classic is lesion to the contralateral STN but can also occur with thalamic or BG lesions
- Athetosis: some view this as variant of chorea, others argue it is a form of dystonia
 - Slow writhing movements typically involving distal extremities



Chorea differential diagnosis tree



Acquired causes of chorea

- Structural lesion
 - Stroke, tumor, demyelinating disease
- Infectious
 - Toxoplasmosis
 - HIV encephalopathy
 - Prion disease
- Autoimmune/paraneoplastic
 - Sydenham chorea
 - Rheumatologic disease: lupus, antiphospholipid antibody syndrome, Sjogren syndrome, Celiac disease, Behcet disease
 - Autoimmune: anti-CRMP-5, anti-NMDA receptor, anti-Hu (ANNA-1), anti-Yo, anti-LGI1, anti-CASPR2, anti-GAD65, anti-IgLON5
- Toxic metabolic
 - Nonketotic hyperglycemia
 - Hypocalcemia, hypoparathyroidism
 - Hyponatremia/hyponatremia
 - Uremia
 - Hypomagnesemia
 - Carbon monoxide poisoning
 - Manganese toxicity (liver failure)
 - Mercury poisoning
 - Organophosphates
 - Polycythemia (static with toxic injury to basal ganglia)
- Drug induced
 - Antiseizure medications (carbamazepine, ethosuximide, lamotrigine, phenytoin, phenobarbital, valproic acid, zonisamide)
 - Levodopa
 - Psychostimulants: Cocaine (“crack-dancing”), Amphetamine
 - Lithium
 - Antidepressants (fluoxetine, fluvoxamine, paroxetine, TCA)
 - Antihistamines (cyproheptadine, diphenhydramine)
 - Anticholinergics
 - Calcium channel blockers (flunarizine, verapamil)
 - Neuroleptic withdrawal
 - Digoxin
 - Baclofen
 - Oral contraceptives, estrogen replacement therapy
 - Steroids
 - Methotrexate
 - Mefenadone
 - Fluoroquinolones



Huntington disease

- The most common genetic cause of chorea in adults is HD
- Features
 - Eye movements:
 - Delayed initiation of saccades is the hallmark oculomotor abnormality
 - Impaired anti-saccade task
 - Ask the patient to look to the side contralateral to the side in which the examiner is holding up a finger. HD patients will tend to look to ipsilateral side, indicating frontal disinhibition
 - Movement disorder: chorea then akinetic rigid syndrome
 - May also see dystonia, myoclonus
 - Cognitive impairment
 - Subcortical dementia, disinhibition, short term memory loss
 - Psychiatric features
 - Depression, anxiety, apathy, aggression, psychosis, OCD
- MRI shows caudate atrophy



Huntington disease

- Autosomal dominant disorder due to CAG repeat expansion in the HTT (IT14) gene on chromosome 4p encoding huntingtin protein
 - Mutation causes toxic gain of function, protein plays role in development
- Individuals with ≥ 40 CAG repeats have complete penetrance with an inverse correlation between the number of repeats and the age at onset
- Lower repeat numbers present later in life
- Individuals with 36 to 39 repeats have variable penetrance of disease
- Anticipation occurs when unstable CAG repeats are inherited from the father due to CAG repeat instability during spermatogenesis
- Children with manifest HD typically have 50 to 60 CAG repeats or more and in contrast with adult onset form, juvenile HD (onset at younger than 20 years of age) presents with parkinsonism and dystonia rather than chorea, and seizures (Westphal variant)



Video of chorea



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Division of Movement
Disorders

Movement Disorders Video Rounds (MOVRS) **June 23rd, 2023**

Case #2

Patient: SL. 71-year-old female

Date: June 22nd, 2023



Sydenham chorea

- Most frequently occurs in children or teens following acute rheumatic fever (group A beta hemolytic streptococci infection throat)
- Molecular mimicry
- Medical issues: carditis, arthritis, subcutaneous nodules , erythema marginatum
- Occurs one to 8 months after the infection
- May present with hemichorea in up to 30% cases
- May co-occur with tics, irritability, psychiatric distress
- Usually spontaneously resolves (can take months to a year or so)
- Treatment with certain medications may be restricted to patient with significantly impaired function from severe chorea
- Workup:
 - Throat culture to ensure no recurrent infection with group A streptococci
 - antistreptolysin O (ASO) and antideoxyribonuclease (antiDNase) titers for preceding strep A infection—positive for months and rising titers suggests recent infection
 - inflammatory markers of crp and ESR



Benign hereditary chorea (brain-lung-thyroid syndrome)

- Most common genetic cause of chorea in children
- Autosomal dominant disorder due to mutation in the NKX2-1 gene encoding thyroid transcription factor-1
- Chorea usually begins in infancy or early childhood, and usually no or minimal progression occurs, with plateauing in adulthood
- Rare remission
- Other features: ataxia, dystonia, hypotonia
- As NKX2-1 gene (thyroid transcription factor) also has role in lung and thyroid development, neonatal respiratory distress, interstitial lung disease, congenital hypothyroidism, thyroid agenesis can occur



Treatment of chorea

- Specific therapies
 - Glycemic control for nonketotic hyperglycemia
 - Phlebotomy and hydroxyurea in polycythemia vera
 - Immunotherapy for autoimmune chorea
 - Detection and removal of cancer for paraneoplastic
- Dopamine depleting drugs (VMAT2 inhibitors)
 - prevent packaging of monoamines into presynaptic storage vesicles, so less dopamine released from presynaptic terminals
 - Tetrabenazine
 - Deutetrabenazine
 - Valbenazine
- Dopamine receptor blocking drugs (D2 receptor blockade)
 - Typical include haloperidol
 - Atypical such as olanzapine or risperidone (greater D2 blockade)
 - Watch for parkinsonism, tardive dyskinesia, metabolic syndrome
- Amantadine (NMDA receptor antagonist): limited data for chorea other than Ldopa induced



Tics

- Sudden, rapid, recurrent, nonrhythmic motor movements or vocalizations
- Premonitory urge that resolves when the tic is done
 - Mounting tension, pressure, itch or feeling localized to region of tic
- Suppressed when engrossed
- Exacerbated by stress, anxiety, anger, infection
- Often can suppress the tic but effort may cause increased stress or exacerbate premonitory sensation “Unvoluntary” rather than involuntary
- Motor or vocal tics



Tourette syndrome

- Onset before age 21
- Motor and vocal tics
- Some terms
 - Echopraxia; imitating observed movements
 - Copropraxia: obscene gestures
 - Vocal tics can include grunting, barking, hoots, spitting
 - Palilalia: repeating ones own words
 - Coprolalia: obscene words
- Comorbidities: ADHD, OCD, anxiety and depression



Treatment of Tourette syndrome/tics

- Alpha adrenergic agents:
guanfacine, clonidine
- Dopamine receptor blockers
- Dopamine depleting agents
(vesicular monoamine transporter-2 inhibitors)
 - Blocking the transport of dopamine into presynaptic vesicles thereby depleting levels at the synaptic terminal
- Benzodiazepines
- Topiramate
- Deep brain stimulation



Myoclonus

- Brief, “lightening”-like muscle jerks –fastest and briefest hyperkinetic disorder
- Asterixis: negative myoclonus
- Classification:
 - Physiologic (sleep jerks, hiccups)
 - Essential (+/- familial)
 - Epileptic (myoclonus + other seizure types)
 - Symptomatic (most common)—secondary to medical or neurologic illness
 - Toxic/metabolic encephalopathy – renal failure, hepatic failure
 - Post-anoxic
- Evaluation: medical history, electrolytes, glucose, renal and liver function tests, drug and tox screen, EEG, MRI brain



Ataxia

- Ataxia is incoordination of muscle movement
 - Clumsy gait, walking as if “drunk,” imbalance
 - Wide-based gait
 - May start as difficulty climbing stairs or running, tendency to fall
 - Variability in stride length or rate, veering to one side
 - Incoordination of limbs
 - Dysmetria
 - Dysdiadochokinesia
 - Heel to shin impaired
 - Ataxic speech
 - Eye movement abnormalities
 - Oscillopsia: world is moving, delayed focusing when moving eyes, problems focusing while driving, difficulty looking up
 - Nystagmus, saccadic intrusions on smooth pursuit, square wave jerks, hypermetric and hypometric saccades
- Evaluation and treatment: MRI brain (look for stroke, structural lesions) and refer to neurology



Video of Ataxia



Brigham and Women's Hospital
Founding Member, Mass General Brigham

Division of Movement
Disorders

Movement Disorders Video Rounds (MOVRS) **March 24th, 2023**

Case #1

Patient: SK. 25-year-old female

Date: March 2nd, 2023



Question 1

A 60-year-old woman is evaluated for a 1 year history of tremor. The tremor affects both arms and is symmetric. She has type II DM, HTN, and gastroparesis. Medications are insulin glargine, insulin lispro, lisinopril, and metoclopramide. On exam she has masked facies, slow movements, and mild bilateral symmetric rigidity in the arms and legs. There is a symmetric resting as well as postural tremor in both arms.

What is the most likely diagnosis?

- A. Progressive supranuclear palsy
- B. Essential tremor
- C. Parkinson disease
- D. Drug induced parkinsonism
- E. Multiple system atrophy



Question 1: Answer

D. Drug-induced parkinsonism

Explanation: There are no red flags in the history or exam to support a diagnosis of either progressive supranuclear palsy (e.g. early falls, gaze palsy, dementia) or multiple system atrophy (e.g. ataxia, autonomic dysfunction). Her exam demonstrates significant parkinsonism, excluding a diagnosis of essential tremor. Parkinson's disease is a consideration, but the postural tremor and the very symmetric nature of the onset, combined with the history of metoclopramide usage makes drug-induced parkinsonism more likely. Metoclopramide should be discontinued, and she should be monitored for improvement.



Question 2

A 72-year-old woman presents with 10 years of progressive action tremor in both arms. Her handwriting is large and shaky, and she cannot hold a cup of coffee without spilling it. She is afraid she has Parkinson disease. On exam she has mild tremor present with arms extended and during finger to nose testing. There is no resting tremor and tone is normal.

What is the most appropriate treatment for her tremor?

- A. Primidone
- B. Carbidopa-levodopa
- C. Gabapentin
- D. Topiramate
- E. Ropinirole



Question 2: Answer

A. Primidone

Explanation: This woman presents with essential tremor. Of the options listed, only primidone is a first-line agent. Topiramate and gabapentin are second-line agents. Carbidopa-levodopa and ropinirole are treatments for Parkinson's disease and not appropriate here.



Thank you



References

- Wirdefeldt K, Adami HO, Philip C, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol* 2011;26(suppl 1):S1-S58.
- Hamza TH, et al. Genome-Wide Gene-Environment Study Identifies Glutamate Receptor Gene CRIN2A as a Parkinson's Disease Modifier Gene via Interaction with Coffee. *Plos Genet* 2011;7(8):e1002237.
- Postuma RB, Berg D, Stern M et al. MDS Clinical Diagnostic Criteria for Parkinson Disease. *Mov Disord* 2015 Jul; 30(12):1591-1599.
- Kalia LV and Lang AE. Parkinson's disease. *Lancet* 2015; 386:896-912.
- Hornykiewicz O. The discovery of dopamine deficiency in the parkinsonian brain. *J Neural Transm Suppl* 2006;9.
- Shin HW, Chung SJ. Drug-induced parkinsonism. *J Clin Neurol* 2012 Mar;8(1):15-21.
- Miyamoto T, Miyamoto M, Inoue Y, Usui Y, Suzuki K, Hirata K. Reduced cardiac 123I-MIBG scintigraphy in idiopathic REM sleep behavior disorder. *Neurology* 2006 Dec, 67(12) 2236-2238.
- The Synuclein-One Study: skin biopsy detection of phosphorylated alpha-synuclein for diagnosis of synucleinopathies. *Neurology*. 2023;100(17 suppl 2). 2023 Annual Meeting Abstracts.
- Gibbons C. Wang N. Rajan S. et al. Cutaneous alpha-synuclein deposition across the synucleinopathies. *Neurology*. 2020;94(suppl15). 2020 Annual Meeting Abstracts.
- Coupland CAC, Hill T, Tom D, et al. Anticholinergic drug exposure and the risk of dementia: a nested case-control study. *JAMA Intern Med* 2019;179(8):1084-1093.
- Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. *Lancet* 1999;354(9192):1771-1775.
- Pantelyat A. Progressive Supranuclear Palsy and Corticobasal Syndrome. *Continuum Movement Disorders* 2022 (28) no 5. 1364-1378.
- Louis ED, Ferreira JJ. How common is the most common adult movement disorder? An update on the worldwide prevalence of essential tremor. *Mov Disord* 2010 Apr 15;25(5):534-41.
- Ondo WG. Current and emerging treatments of essential tremor. *Neurol Clin* 2020;38(2):309-323.
- Albanese A, Bhatia K Bressman SB et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 203;28(7):863-873.

