NOTES
MOVEMENT DISORDERS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Disorders causing abnormal movement
  - Increased voluntary/involuntary movement (hyperkinetic disorders); reduced movement (hypokinetic disorders)

TYPES

Acute fulminant episodes

- Reaction to trigger, medication (neuroleptic malignant syndrome)

Benign chronic conditions

- Restless legs syndrome (RLS), essential tremor

Progressive chronic syndromes

- Parkinson's disease (PD), Friedreich's ataxia

CAUSES

- Often idiopathic; genetic mutations, medication

SIGNS & SYMPTOMS

- Mild, unpleasant sensations, intention/action tremors; rigidity, catatonia
- Motor abnormality
  - *Hypokinesia:* ↓ amplitude
  - *Bradykinesia:* ↓ speed
  - *Dyskinesia:* unwanted, characterized motor movement
  - *Tremor:* rhythmic motor movement; resting, action, postural
  - *Rigidity:* abnormal, uncoordinated muscle tone across joint

DIAGNOSIS

OTHER DIAGNOSTICS

- Neurologic examination
  - Observation of spontaneous movement, strength testing, tone evaluation, reflex exam

TREATMENT

MEDICATIONS

- Beta blockers, anti-epileptics, benzodiazepines; dopamine replacement, agonists

OTHER INTERVENTIONS

- Avoid caffeine, nicotine, etc.
- Educational, supportive therapy

ESSENTIAL TREMOR

osms.it/essential-tremor

PATHOLOGY & CAUSES

- Most common movement disorder; involuntary, rhythmic shaking
- Usually affects hands, fingers; sometimes head, vocal cords
- Action tremor (occurs during muscle effort)
  - Postural/intention tremor

CAUSES

- Unknown; may be familial with autosomal dominant inheritance pattern

RISK FACTORS

- Meat consumption
  - Exposure to heterocyclic amines (e.g. harmane, harmaline)
- Associated with dystonia (cervical, spasmodic, cranial dystonia, writer's cramp), parkinsonism

SIGNS & SYMPTOMS

- Rhythmic, symmetrical tremor
  - Hands, head, vocal cords, neck, face, leg, tongue, trunk
- High frequency tremor (4–12Hz) exacerbated by muscle contraction
- Inability to perform precise tasks
- Intention tremor
  - Intensifies upon touching nose with finger
- Postural tremor
  - During outstretched arms
- Walking difficulties
- ↓ tremor with alcohol intake

DIAGNOSIS

OTHER DIAGNOSTICS

- Postural/action tremor of hands/head; duration ≥ three year
- Alleviation with alcohol intake

Physical examination

- Fine postural, action tremor in hands, head/voice
- *Asymmetric/symmetric:* cogwheel rigidity, resting tremor, dystonia (esp. head)

TREATMENT

MEDICATIONS

- If disabling, symptomatic treatment
  - Beta blockers
  - Anti-epileptics
  - Benzodiazepines
  - Botulinum toxin (head tremors not responsive to medication)

OTHER INTERVENTONS

- Avoid caffeine, nicotine, etc.
- Get enough sleep

ESSENTIAL TREMOR VS. PARKINSON'S TREMOR

	ESSENTIAL TREMOR	PARKINSON'S TREMOR
LATERALLY	Symmetrical	Asymmetrical
KINETICS	Movement/posture	Resting
SPEED	High frequency	Slow frequency
INVOLVEMENT	Arms, legs, voice, neck, face, tongue	Hands, legs, chin

FRIEDREICH'S ATAXIA

osms.it/friedreichs-ataxia

PATHOLOGY & CAUSES

- Genetic disorder; causes progressive central nervous system (CNS) damage, movement problems
- Predominantly affects CNS; also affects heart, pancreas
- ↓ frataxin → ↓ mitochondrial oxidative phosphorylation → cell damage, death
- ↓ frataxin → ↑ free iron → ↑ oxidative stress → cell damage, death
- Neuronal cell death affects posterior columns of spinal cord, distal corticospinal tracts, spinocerebellar tracts, brain stem, cerebellum
- Gene silencing → no frataxin synthesized → iron accumulates in cell, reacts with oxygen → unstable oxygen radicals → cell death

CAUSES

- Trinucleotide repeat GAA expansion (chromosome 9q13) → ↓ production of mitochondrial inner membrane protein, frataxin
  - Autosomal recessive inheritance pattern
  - ↑ repeats → ↑ severity, ↓ age of onset
  - 600–1200 trinucleotide repeats → Friedreich's ataxia

COMPLICATIONS

Progressive loss of cells

- In CNS, heart, pancreas
- Limb, gait ataxia → wheelchair bound → bedridden
- Dysphagia, dysarthria → aspiration → gastric bacteria insult to respiratory parenchyma
- Hypertrophic cardiomyopathy (secondary to myocardial cell death)
  - Fibrosis → arrhythmia, hypertrophic cardiomyopathy → heart failure
  - Most common cause of death in affected individuals (age 40–50)
- Diabetes mellitus
  - Loss of beta cells of pancreas
- 25% of affected individuals
- Musculoskeletal abnormalities
  - Muscle denervation → abnormal forces about joints → abnormalities
- Kyphoscoliosis
  - Severe → ↓ total lung capacity → restrictive lung disease

- Pes cavus
  - Similar restrictive lung disease in severe cases
- Hammer toes

SIGNS & SYMPTOMS

- Ataxia
  - Falling/staggering while walking, wide-based gait
  - Gait ataxia most common (age 0–10); most individuals progress to wheelchair dependence within 11–25 years
- Loss of vibratory sense, proprioception
- Muscle weakness, chest pain, dyspnea, heart palpitations, absence of tendon reflexes in legs, involuntary eye movements, action tremor, hand clumsiness, dysarthria, fatigue

DIAGNOSIS

LAB RESULTS

Genetic testing

- Confirms diagnosis
- GAA repeats; examine first intron in frataxin gene

OTHER DIAGNOSTICS

- Symptom progression, family history
- Neurological exam
  - Ataxia (gait, hand); ↓ vibratory sensation, proprioception; ↓ deep tendon reflexes, nystagmus

Electromyogram

- Absent/reduced sensory nerve action potentials
- Normal/only slightly decreased motor nerve conduction velocities
- Abnormal auditory, visual, somatosensory-evoked responses

TREATMENT

OTHER INTERVENTIONS

- Occupational, physical therapy
  - Balance, ataxic progression
- Cardiology
  - Annual electrocardiogram, echocardiogram
- Severe scoliosis
  - Orthopedic referral
- Annual diabetes screening
- Genetic, psychological counseling services

NEUROLEPTIC MALIGNANT SYNDROME

osms.it/neuroleptic-malignant-syndrome

PATHOLOGY & CAUSES

- Life-threatening idiosyncratic reaction to antipsychotic drugs; muscle rigidity, fever, altered mental status, autonomic dysfunction
- Dopamine blockade theory
  - Central dopamine blockade → hypothalamus → hyperthermia, dysautonomia
  - Nigrostriatal dopamine blockade → tremor, rigidity
- Peripheral muscle theory
  - Direct toxic effect of neuroleptics → mitochondria of skeletal muscle → rigidity, fever
- Sympathetic nervous system theory
  - ↓ dopamine inhibitors → ↑ sympathetic output
  - ↑ sudomotor, vasomotor activity → fever

CAUSES

Reaction to medications

- First-generation neuroleptic (most common)
  - Haloperidol, fluphenazine, chlorpromazine
- Second-generation neuroleptic medication
  - Clozapine, risperidone, olanzapine
- Antiemetic
  - Metoclopramide, promethazine, droperidol
- Withdrawal of L-Dopa/dopamine agonist therapy (Parkinson disease)

RISK FACTORS

- Increase in dose/change of neuroleptic medication
- Abrupt cessation/reduction of dopaminergic medication
- Lithium/alcohol/psychoactive substance use
- Previous episode of neuroleptic malignant syndrome
- Acute injury (e.g. trauma, surgery, infection)
- Psychiatric conditions (e.g. acute catatonia, severe agitation)
- Lewy body dementia

COMPLICATIONS

- Rhabdomyolysis, renal failure
- Seizures
  - Due to hyperthermia, metabolic imbalances
- Encephalopathy, stupor, coma
- Cardiac arrhythmias (e.g. torsades de pointes, cardiac arrest)
- Disseminated intravascular coagulation

SIGNS & SYMPTOMS

Altered mental status

- Agitated delirium with confusion (initial symptom); coma

Muscular abnormalities

- Generalized muscular rigidity ("lead-pipe rigidity")
  - Associated dysphonia, dysarthria
- Catatonic signs
- Extrapyramidal symptoms
  - Tremor, chorea, akinesia
- Less common
  - Dystonic movements (e.g. opisthotonos, trismus, blepharospasm), mutism, dysarthria, dysphagia

Hyperthermia

- Temperatures > 38–40°C/100.4–104°F

Autonomic dysfunction

- Tachycardia, labile/elevated blood pressure, tachypnea, sialorrhea, profuse diaphoresis (sweating), flushing, incontinence

DIAGNOSIS

LAB RESULTS

- Severe ↑ creatine kinase (CK)
  - Correlates with rigidity severity → 1–100k international units/L
- Mild ↑ lactate dehydrogenase, alkaline phosphatase, liver transaminases
- Electrolyte imbalances
  - ↓ Ca^{2+}, ↓ Mg^{2+}, ↓ Na^{+}/↑ Na^{+}, ↑ K^{+}, metabolic acidosis
- ↑ white blood cell count (leukocytosis) 10–40k
- Myoglobinuria
- ↓ serum iron concentration

OTHER DIAGNOSTICS

- Clinical presentation
  - Altered mental status → hyperthermia, rigidity → autonomic dysfunction

TREATMENT

MEDICATIONS

- Discontinue offending neuroleptic agent
- Dantrolene (skeletal muscle relaxant), bromocriptine (dopamine agonist); both (if severe) to reduce muscle rigidity, hyperthermia

OTHER INTERVENTIONS

- Maintain cardiorespiratory stability
  - Intubation, mechanical ventilation
- Temperature reduction
  - Cooling blankets, ice water gastric lavage, ice packs in axilla; acetaminophen/aspirin
- Correct fluid, electrolyte imbalance
  - ↓ CK damage/accumulation; replete insensible losses from diaphoresis
  - *Benzodiazepines:* ↓ uncontrollable agitations
- Electroconvulsive therapy
  - If not responsive to medical therapy in first week; if severe/lethal catatonia

NEUROLEPTIC MALIGNANT SYNDROME VS. SEROTONIN SYNDROME

	HISTORY	CLINICAL MANIFESTATION	LAB RESULTS	DISTINGUISHING FEATURES
NEUROLEPTIC MALIGNANT SYNDROME	Neuroleptic use	Tetrad: mental status change, fever, rigidity, autonomic instability	↑ CK, leukocytosis, metabolic abnormalities	Severe rigidity, hyperthermia
SEROTONIN SYNDROME	SSRI use	Mental status change, neuromuscular hyperreactivity (tremor, myoclonus), autonomic instability	None consistent with disease; ↑ CPK, leukocytosis, ↓HCO_3^-	Prodrome of N/V/D; shivering, myoclonus, hyperreflexia, ataxia

PARKINSON'S DISEASE

osms.it/parkinsons-disease

PATHOLOGY & CAUSES

- Degeneration of dopaminergic neurons in substantia nigra → tremor, rigidity, akinesia, postural instability
- Most common neurological disorder; onset after age 50
- Degeneration of neurons in substantia nigra → dopamine depletion from basal ganglia → disruption of connection to thalamus, motor cortex → Parkinsonism
- Exact mechanism unknown; build-up of abnormal proteins into Lewy bodies in neurons; accompanied by death of astrocytes, significant increase in microglia of substantia nigra
- Protein (e.g. alpha-synuclein) accumulation in neuron → abnormal intracellular transit → neuronal damage, death → motor symptoms
  - *Asymptomatic neuronal degeneration:* brainstem (locus coeruleus)
  - *Symptomatic neuronal degeneration:* basal ganglia; dopaminergic substantia nigra pars compacta neurons diseased, die → dennervate striatum → dysfunctional basal ganglia → hypo/bradykinetic motor output
  - *Late degeneration:* cerebral cortex; leads to cognitive impairment

CAUSES

- Usually idiopathic
- Mutation of *PINK1*, parkin, alpha synuclein genes
- Toxicity in recreational drug MPPP (synthetic opioid); rare

RISK FACTORS

- Family history, previous head injuries, pesticides exposure
- Protective factors
  - Caffeine, nicotine

COMPLICATIONS

- Freezing phenomenon
  - Progressive hypokinesia, bradykinesia → (akinetic) pauses in movement; common when walking; tend to occur at thresholds (e.g. door frames)
- Falls
  - Secondary to postural instability, poor movement amplitude
- Dystonia
  - Abnormal tone across joints → disfiguring, painful posturing; universal flexion of joints → severely kyphotic posturing → poor ability to ambulate, ventilate
- Dementia
  - Common after prolonged, primarily motor disease (in contrast to Lewy body dementia); psychosis, hallucinations (severe)

SIGNS & SYMPTOMS

- Psychiatric
  - Depression, anxiety, mood disturbances; impairment of cognitive function, dementia (advanced stages)
- Sleep disturbances
  - Wild dreams
- Autonomic dysfunction
  - Orthostatic hypotension, constipation, increased sweating
- ↓ olfactory sense
  - Common first symptom; history of ↓ / changed sense of taste, smell prior to motor symptoms
- Micrographia

MNEMONIC: TRAPS

Parkinson's disease symptoms

Tremor (resting tremor)
Rigidity
Akinesia
Postural changes (stooped)
Stare (serpentine stare)

PARKINSON'S DISEASE IMPAIRMENTS

MOTOR IMPAIRMENTS	NON-MOTOR IMPAIRMENTS
- Tremor - Rigid muscles - Difficulty walking - Decreased balance - Freezing of movement - Slowness, decreased amplitude of movement	- Cognitive impairment - Depression, anxiety - Sleep difficulties - Mood disturbances - Decreased motor learning ability

DIAGNOSIS

OTHER DIAGNOSTICS

- Clinical presentation
  - Resting tremor, rigidity, bradykinesia
  - Dopaminergic medication response
- Postmortem autopsy
  - Loss of pigmented dopaminergic neurons of substantia nigra pars compacta
  - Lewy bodies (intracytoplasmic eosinophilic inclusions), neurites

TREATMENT

MEDICATIONS

- Symptomatic treatment; see mnemonic

MNEMONIC: SALAD

Common Parkinsonism treatments

Selegiline
Anticholinergics: trihexyphenidyl, benzhexol, orphenadrine
L-Dopa + peripheral decarboxylase inhibitor: carbidopa, benserazide
Amantadine
Dopamine postsynaptic receptor agonists: bromocriptine, lisuride, pergolide

Dopamine replacement

- Precursor to dopamine → ↑ dopamine synthesis → ↑ synaptic dopamine → ↓ motor symptoms
- Commonly formulated with carbidopa (peripheral decarboxylase inhibitor)
  - Carbidopa-mediated inhibition of liver, systemic carboxylation → levodopa cross blood brain barrier (BBB) → ↑ dopamine formation
- Adverse effects
  - *On/off phenomena:* return of symptoms prior to next dose; due to half life of levodopa (approx. 90 minutes)
  - *Dyskinesia, dystonia:* abnormal, repetitive movement (dyskinesia), abnormal sustained muscle contraction (dystonia); head, neck (e.g. tardive dyskinesia of tongue, cervical torticollis); ↑ incidence with ↑ dosing, duration of disease
  - *Neuroleptic malignant syndrome:* when discontinued abruptly/high, multiple doses missed

Dopamine agonists

- ↑ dopaminergic stimulation of postsynaptic receptors → ↓ motor symptoms
- Adverse effects
  - Dyskinesia
  - *Impulse control disorder:* ↑ risk-taking behavior (e.g. pathologic gambling; compulsive sexual behavior, shopping)

Monoamine oxidase B (MAO-B) inhibitors

- ↓ MAO-B-related dopamine metabolism → ↑ synaptic dopamine → ↓ motor symptoms
- Most effective for mild-moderate symptoms

Anticholinergic

- Improves neurochemical imbalance in basal ganglia
- Most useful in young (< 70) individuals with tremor as primary symptom; less useful for rigidity, bradykinesia
- Anticholinergic side effects common

Amantadine

- Antiviral drug
  - Known NMDA receptor agonist; ↓ neurotransmitter imbalance i
- Most useful in mild disease

Catechol-O-methyltransferase (COMT) inhibitors

- ↓ dopamine, levodopa metabolism → ↑ synaptic dopamine → ↓ motor symptoms
- Rarely used as monotherapy

SURGERY

- Deep brain stimulation (DBS)
  - Direct neural stimulation of basal ganglia (either subthalamic nucleus of globus pallidus interna) → ↑ motor output of basal ganglia → ↓ motor symptoms
  - Severe/medication nonresponsive disease

OTHER INTERVENTIONS

- Education, support
  - Physical, emotional aspect of degenerative, debilitating disease
- Physical therapy
  - Exercise → ↓ incidence of falls

RESTLESS LEG SYNDROME

osms.it/restless-legs-syndrome

PATHOLOGY & CAUSES

- Uncontrollable urge to move legs, relieved by movement
- Affects legs, feet bilaterally; less commonly affects arms

CAUSES

- Unknown
- CNS
  - ↓ iron, dopamine
- Peripheral nervous system
  - Abnormal A fibers, peripheral nerve microvasculature

TYPES

Primary RLS

- Idiopathic; runs in families; onset < 45 years old; progressive, worsens over time

Secondary RLS

- Associated with underlying medical conditions, medications; onset > 45 years

RISK FACTORS

- Pregnancy, iron deficiency/anemia, smoking, caffeine, Parkinson's disease, family history, renal failure, obesity
- Peripheral neuropathy (due to diabetes, alcoholism, rheumatoid arthritis, etc.)

- Medications
  - Antidepressants, antiemetics, antipsychotics, antihistamines, calcium channel blockers
- More common in individuals who are biologically female

COMPLICATIONS

- Insomnia → daytime drowsiness

SIGNS & SYMPTOMS

- Strong urge to move legs while resting; unpleasant sensations (e.g. tingling, burning, crawling, itching, aching)
- Relief by movement; worsening of symptoms in evening/night → insomnia
- Nighttime leg twitching while asleep

Aggravating factors

- Antihistamines
  - Commonly used for sleep assistance
- Dopamine antagonists
- Psychiatric medications
  - Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs)

DIAGNOSIS

OTHER DIAGNOSTICS

Clinical Presentation

- Urge to move limbs with/without unpleasant sensations
- Improvement with activity
- Worsening at rest/in evening

TREATMENT

MEDICATIONS

- If other interventions not effective
- Dopamine agonists (e.g. pramipexole, ropinirole)
- Alpha-2-delta calcium channel ligands (e.g. pregabalin, gabapentin)
- Benzodiazepine
  - Individuals with intermittent symptoms
- Iron replacement
  - ↓ symptom severity when low (< 75ng/ml) serum iron levels repleted

OTHER INTERVENTIONS

- Lifestyle changes
  - Avoid aggravating factors/situations, ↓ caffeine intake
- Mental alert activities
  - Distract individual in times of symptoms