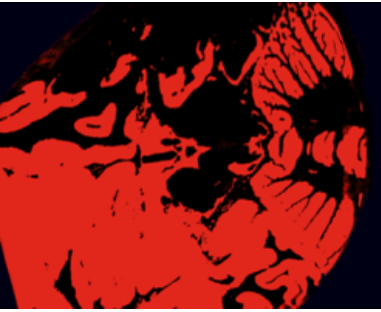

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Differential Diagnosis of Parkinson's Disease, Essential Tremor, and Multiple Sclerosis

Greg Pontone, MD, MHS

Director, Parkinson's Neuropsychiatry Clinical Programs

Johns Hopkins University School of Medicine

Disclosures

Dr. Pontone has consulted for:

- Acadia Pharmaceuticals Inc
- Concert Pharmaceuticals
- Cerevance

Learning Objectives

- Summarize the most common clinical presentations of multiple sclerosis, Parkinson's disease, and essential tremor
- Discuss the differential diagnosis of these three neurological disorders
- Briefly review general treatment strategies and disease modifying therapies

Multiple Sclerosis

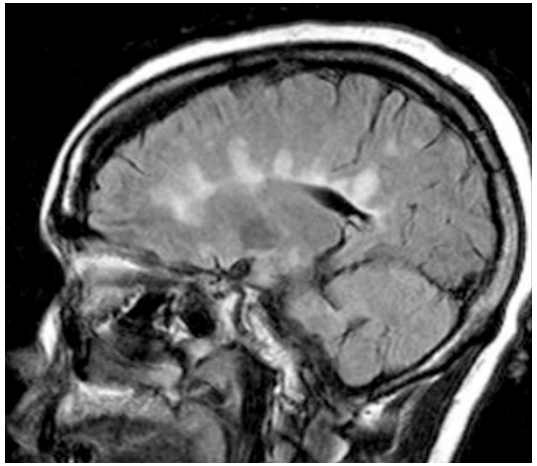
Multiple Sclerosis

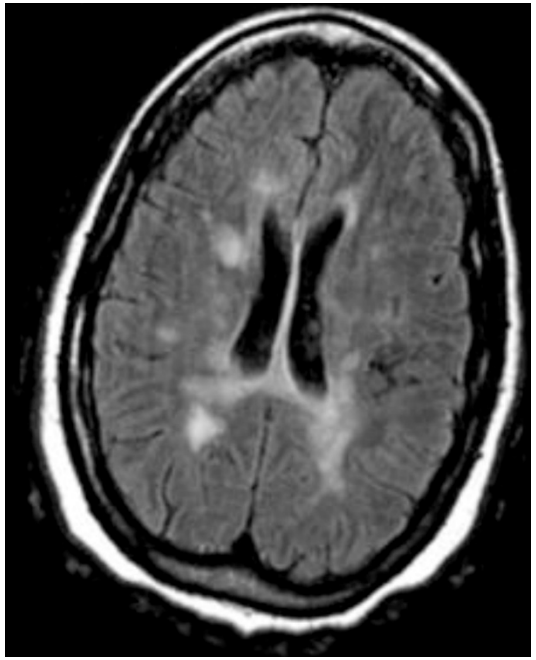
- Incidence and prevalence are increasing globally
- Nearly 3:1 female to male
- Mechanism remains unclear, gene-environment interaction suspected, 1/8 have family history
- Low serum vitamin D, ultraviolet B light, smoking, (childhood) obesity, and infection with Epstein-Barr virus are associated with increased risk
- Migration studies suggest time from exposure to risk factors and onset is 10-20 years
- Organ specific T-cell mediated autoimmune disease
- Two-stage disease with early inflammation responsible for relapsing-remitting disease and delayed neurodegeneration causing non-relapsing progression

Diagnosing Multiple Sclerosis

- Diagnosis is clinical, excluding mimics is key
- Characteristic pathological hallmark of MS is perivenular inflammatory lesions, leading to demyelinating plaques
- Oligodendrocyte damage and demyelination occur as a result of inflammation
- Most common presentations are optic neuritis, brainstem, and spinal cord syndromes
- MS relapses develop over hours to days and last several weeks, with gradual recovery in early disease
- Neuronal reserve is lost over repeat relapses, recovery is incomplete, neurological deficits accrue resulting in increasing disability; MRI often shows brain volume loss compared to controls

MRI of Multiple Sclerosis Lesions





Multiple Sclerosis Subtypes

- Relapsing and remitting multiple sclerosis (RRMS) ~85%
- Secondary progressive multiple sclerosis – develops 10-15 years after RRMS onset in ½
- Primary progressive multiple sclerosis (PPMS) ~10% – progressive disability in one dominant neuronal system (progressive spastic paraparesis, but sensory ataxia, cerebellar ataxia, cognitive and progressive visual failure)
- Neurodegeneration is likely present from clinical onset
- Alternatively, MS as a continuum from radiologically isolated to relapsing to progressive disease

Diagnosing Multiple Sclerosis — Relapsing-Remitting (MacDonald 2017)

Dissemination in space

- 2 or more lesions or 1 lesion with history of a prior attack involving a different CNS site or,
- One or more T2 lesion in at least 2 of 4 MS-typical regions of the CNS

Dissemination in time

- 2 or more attacks separated by at least 1 month, or
- Simultaneous presence of asymptomatic gadolinium enhancing and non-enhancing lesions at any time, or
- New T2 and/or gad-enhancing lesion on follow up compared to baseline, or
- Demonstration of CSF-specific oligoclonal bands

Diagnosing Multiple Sclerosis — Primary Progressive (Macdonald 2010)

1) 1 year of disease progression and

2) 2 out of 3:

- Diffusion in space in brain, 1 or more T2 lesions in at least one MS-typical region
- Diffusion in space in the spinal cord, 2 or more T2 lesions in the cord
- Positive CSF, oligoclonal bands on isoelectric focusing and/or elevated IgG index

Differential Diagnosis of Multiple Sclerosis

Autoimmune disorders: Behcet syndrome, CNS vasculitis, sarcoidosis, systemic lupus, Sjogren syndrome

Hereditary disorders: adrenoleukodystrophy, Refsum disease, spinocerebellar degeneration, CADASIL

Infectious causes: CMV, HIV, human T-lymphotropic virus type 1, HSV, varicella zoster virus, Lyme, syphilis, tuberculosis

Toxic/nutritional syndromes: alcohol, B12, methylmalonic acid, plasma homocysteine, folate

Vascular ischemic event: stroke, TIA, AVM or fistula for spinal, ischemic optic neuritis

Differential Diagnosis of Multiple Sclerosis

- Neuromyelitis optica (NMO)
- Presents with inflammation and demyelination
- Most commonly optic neuritis and transverse myelitis
- Similar to MS may relapse, but little to no progression independent of relapses
- 10:1 women to men; more common in African Americans, Asians, Hispanics
- Criteria for with and without IgG to aquaporin-4 water channel; seropositivity in 75% of patients with NMO clinical symptoms

Differential Diagnosis of Multiple Sclerosis

- Diagnostic lumbar puncture is advised, oligoclonal immunoglobulin G bands or oligoclonal bands
- Anti-nuclear antibody, B12, thyroid function, RPR, HIV at a minimum
- MRI brain and spinal cord if consistent with presentation

Treatments for Multiple Sclerosis

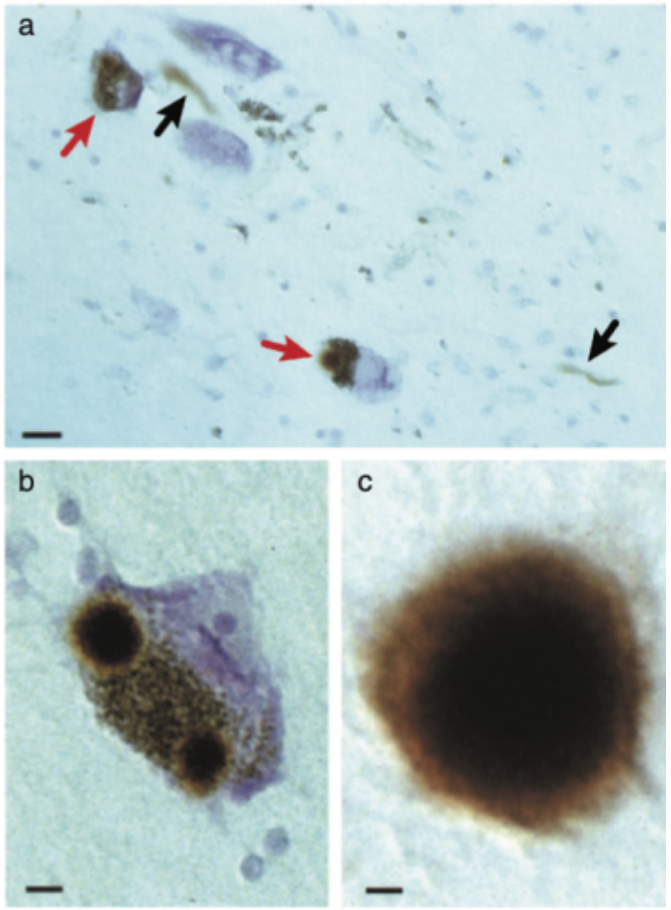
- Disease-modifying therapies
  1) Immunosuppressant — fingolimod, natalizumab, ocrelizumab
  2) Immunomodulatory — interferon beta, glatiramer acetate, teriflunomide
  3) Immune reconstitution therapies —- alemtuzumab and cladribine
- No evidence of disease activity (NEDA)
- Symptomatic therapies
  - Medications and physical therapies for symptoms resulting from CNS damage, eg, medications for bladder dysfunction, medications for neuropathic pain, Sativex for spasticity, fampridine for gait disturbance

Parkinson’s Disease

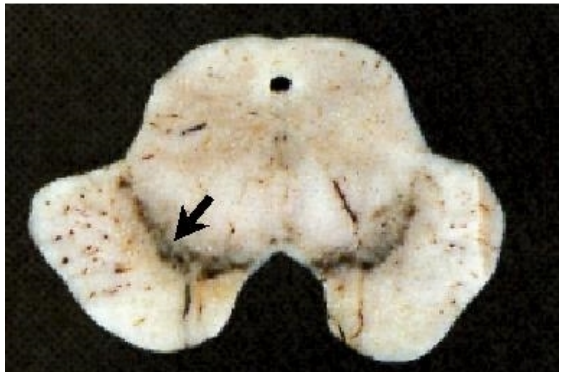
Parkinson's Disease

- Parkinson's disease is a progressive neurodegenerative disorder characterized by aggregates of misfolded α-synuclein called Lewy bodies
- Parkinson's disease has a complex clinical phenotype that includes motor and non-motor symptoms that vary not only in severity but also in terms of presence or absence from case to case

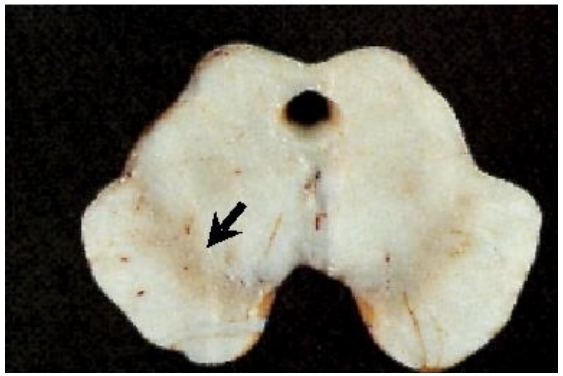
Parkinson's Disease – Substantia Nigra



Normal



Parkinson's



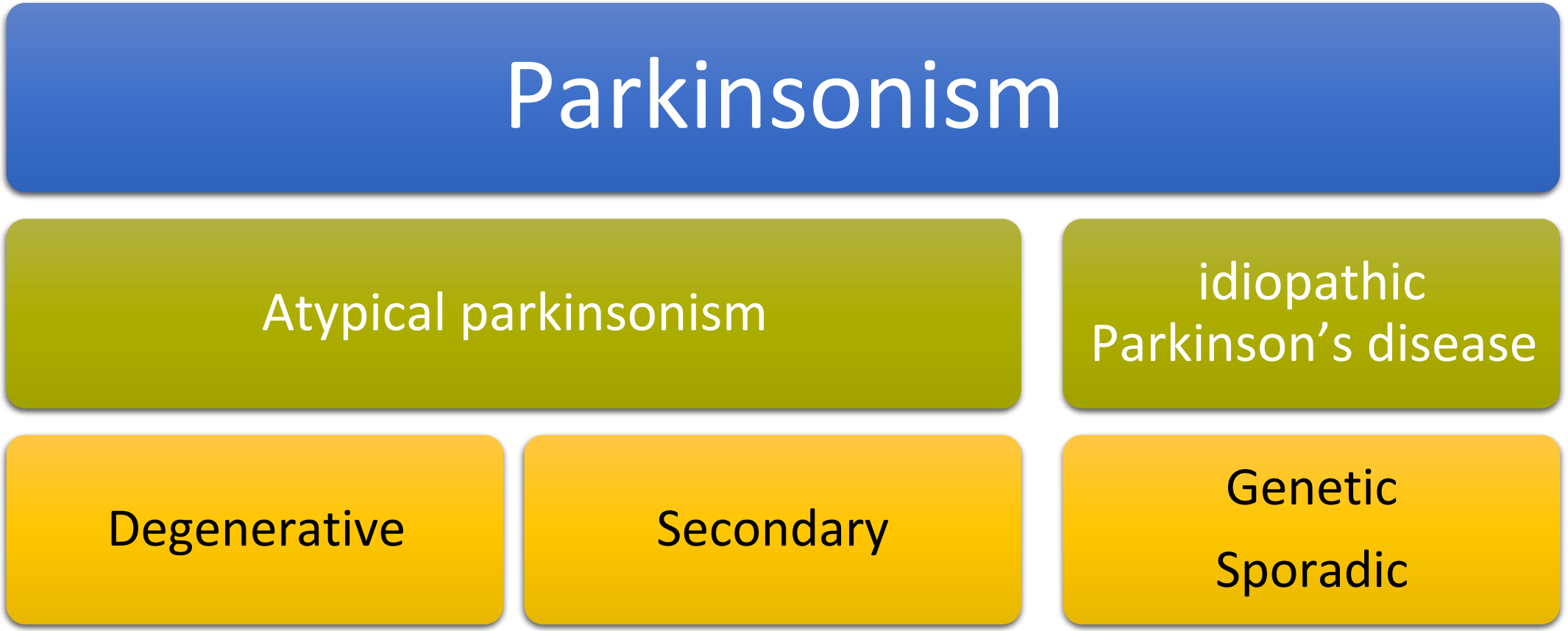
Clinical Diagnosis of PD Requires Only Motor Symptoms

- First essential criterion:
  - Slowing of physical movement (bradykinesia)

- Plus at least one of the following:
  - Tremor (4-7hz)
  - Muscle rigidity

Postuma RB et al Mov Disord 2015

Differential Diagnosis of Parkinsonism



Atypical Parkinsonism — Degenerative

α synucleinopathies
- Multiple system atrophy
- Lewy body dementia

Tauopathies
- Progressive supranuclear palsy
- Corticobasal syndrome
- Other 4 repeat tauopathies

❖Spinocerebellar ataxias (other proteins, CAG repeats) may also be in the differential

Secondary Parkinsonism

Drug induced	Vascular	Encephalitis (von Economo)
Toxic (eg, MPTP)	Hydrocephalus related	Wilson's disease

Differential Diagnosis of Parkinsonism — ‘Absolute Exclusion Criteria’

1. Unequivocal cerebellar abnormalities – cerebellar gait or oculomotor changes, limb ataxia
2. Downward vertical supranuclear gaze palsy or slowing of downward saccades
3. Diagnosis of probable bvFTD or primary progressive aphasia within 5 years of disease
4. Parkinsonism restricted to lower limbs for more than 3 years
5. Use of dopamine receptor blocker or dopamine-depleting agent
6. Absence of response to high-dose levodopa despite at least moderate severity disease
7. Unequivocal cortical sensory loss, clear limb apraxia, or progressive aphasia
8. Normal functional neuroimaging of the presynaptic dopaminergic system
9. Alternative condition is more likely

Differential Diagnosis of Parkinsonism – Red Flags

1. Rapid progression of gait impairment, eg, wheelchair within 5 year onset
2. Absence of progression of motor symptoms
3. Early bulbar dysfunction, severe dysphonia or dysarthria or dysphagia within 5 year onset
4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor
5. Severe autonomic failure in first 5 years
6. Recurrent falls because of impaired balance within 3 year onset
7. Disproportionate anterocollis or contractures of hand or feet within first 10 year
8. Absence of any common nonmotor features despite 5 year disease duration
9. Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness, hyperreflexia
10. Bilateral symmetric parkinsonism

Interventions for Parkinson's Disease

1. Prevention or delay of disease progression ('disease modifying')
2. Symptomatic monotherapy
3. Adjunctive therapies
4. Prevent or delay of motor complications
5. Motor complication therapies

Disease Modifying Interventions

- Exercise – has insufficient evidence and considered investigational, but is widely recommended
- No clinically useful interventions to prevent or delay disease progression (Fox SH et al 2018)
- Notable negative studies – MAOIs, CoQ10, creatine, vitamin D, dopamine agonists
- Promising candidates – BIIB054 (cinpanemab) targets abnormal alpha-synuclein, BIIB094 (LRRK2 ASO) antisense oligonucleotide helps reduce LRRK2 protein, small molecules may also be helpful, agents that down regulate inflammation especially via type-2 astrocytes

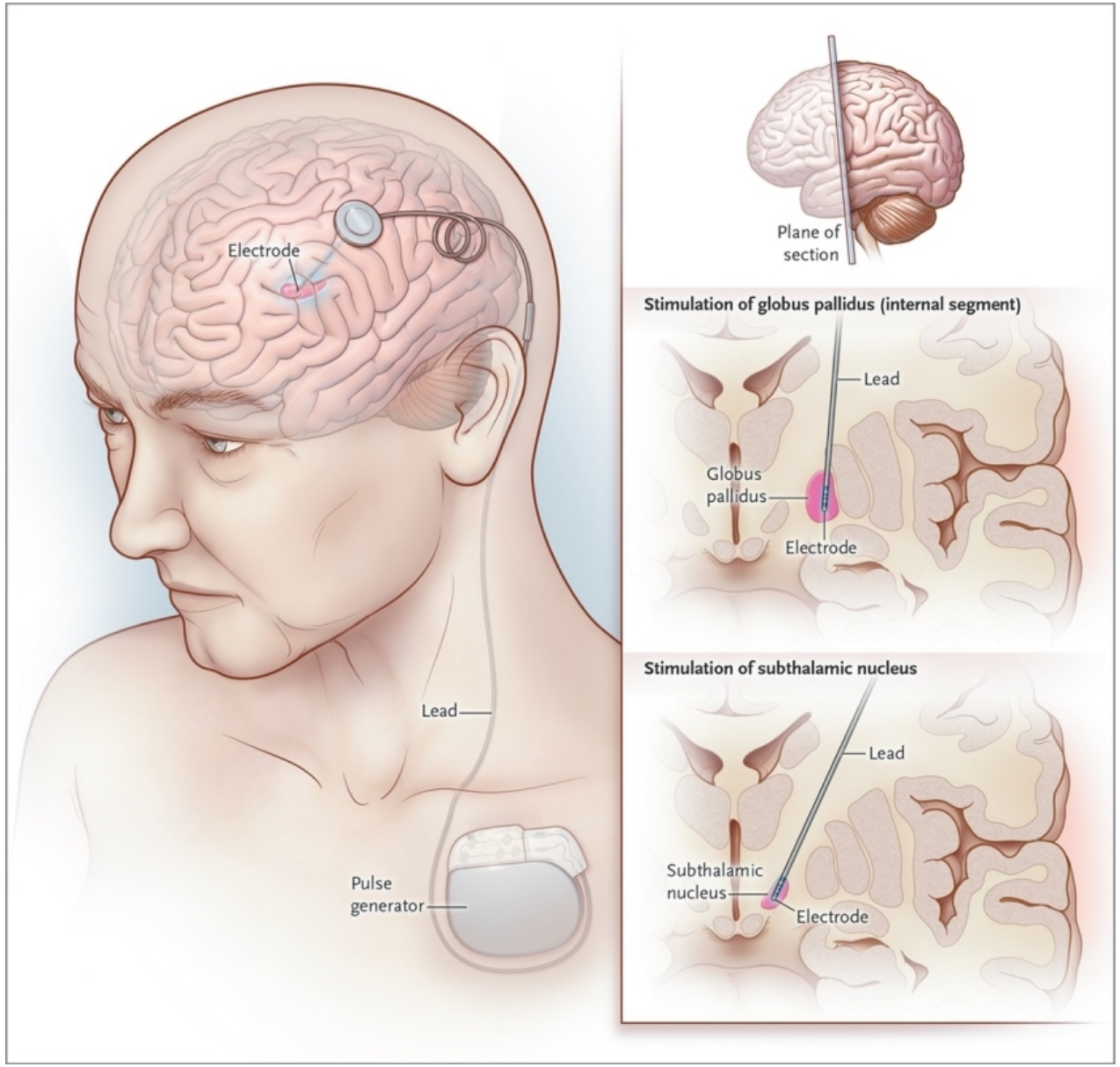
Symptomatic Monotherapy

Efficacious – clinically useful

- Dopamine agonists – non-ergot, ergot
- Levodopa + peripheral decarboxylase inhibitor – immediate release, controlled release, extended release
- Monoamine oxidase inhibitors – B-selective, eg, rasagiline, selegiline

Likely efficacious – clinically useful or possibly useful

- Anticholinergics
- Amantadine



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Essential Tremor

Essential Tremor

- Essential tremor is the most common movement disorder affecting ~1% of the population
- Prevalence increases 5-fold with age; but does occur in children and young adults
- ET is autosomal dominant in at least 60% of patients

Diagnosis of Essential Tremor

- Isolated ‘action’ tremor 6-12 Hz of bilateral upper limbs of at least 3 years duration
- ‘Action tremor’ – postural or kinetic tremor involuntary, rhythmic, oscillatory movement of a body part when maintaining posture or with voluntary movement
- May be accompanied by tremor of head, voice, or lower limbs (less common)
- ‘Isolated’ no other neurologic signs, such as ataxia or parkinsonism
- Amplitude of the kinetic tremor remains constant between targets
- Tremor often temporarily improves with alcohol

Differential Diagnosis of Essential Tremor

- Parkinson's disease
- Drug induced tremor
- Hyperthyroidism
- Wilson's disease (under age 50)

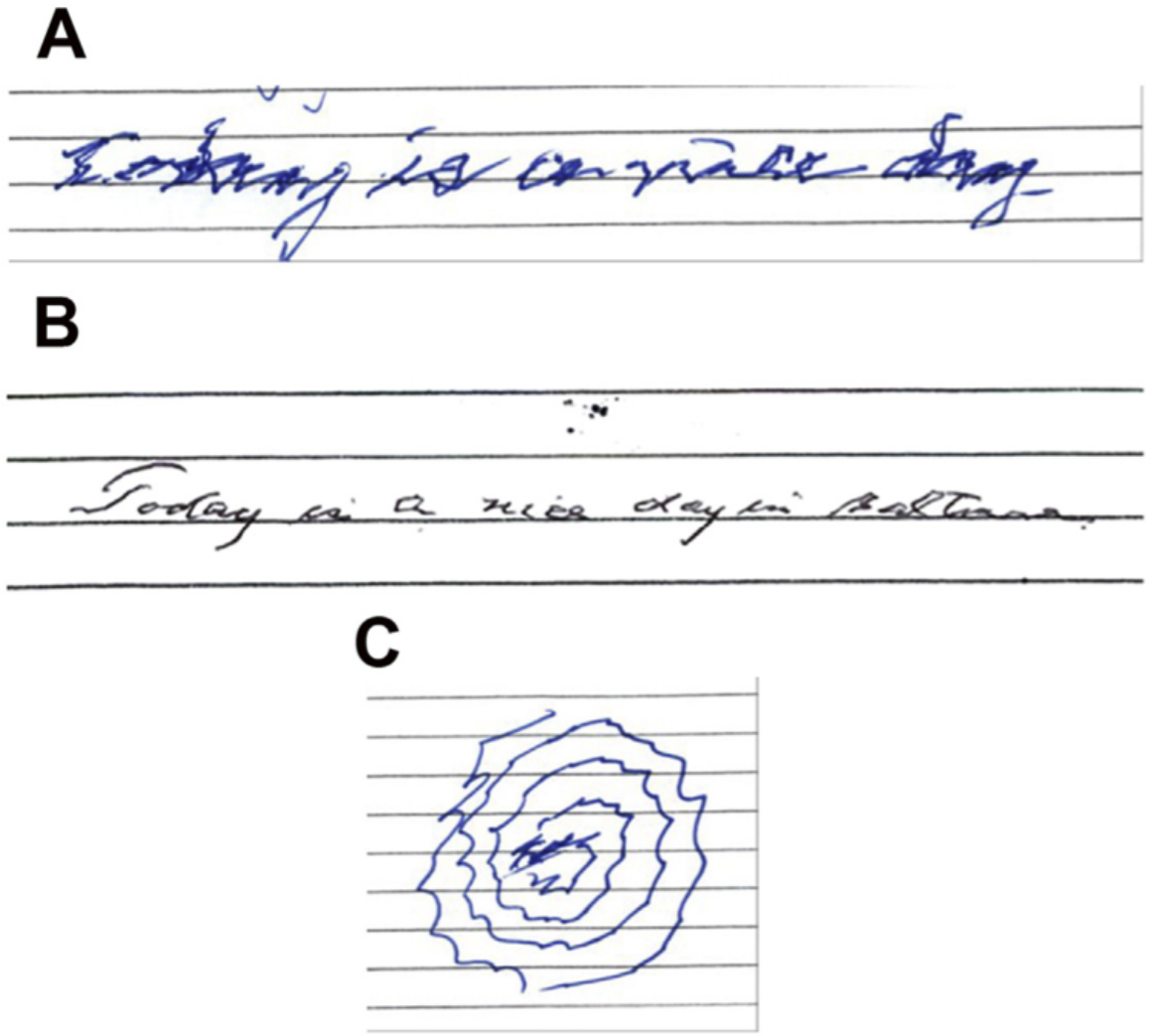
Differential Diagnosis of Essential Tremor

Essential Tremor

- Family history in >60%
- Tremor improves with alcohol
- Action tremor
- Tremor onset is bilateral
- Associated signs absent
- Tremor absent/reduced when walking
- Negative DaTscan*

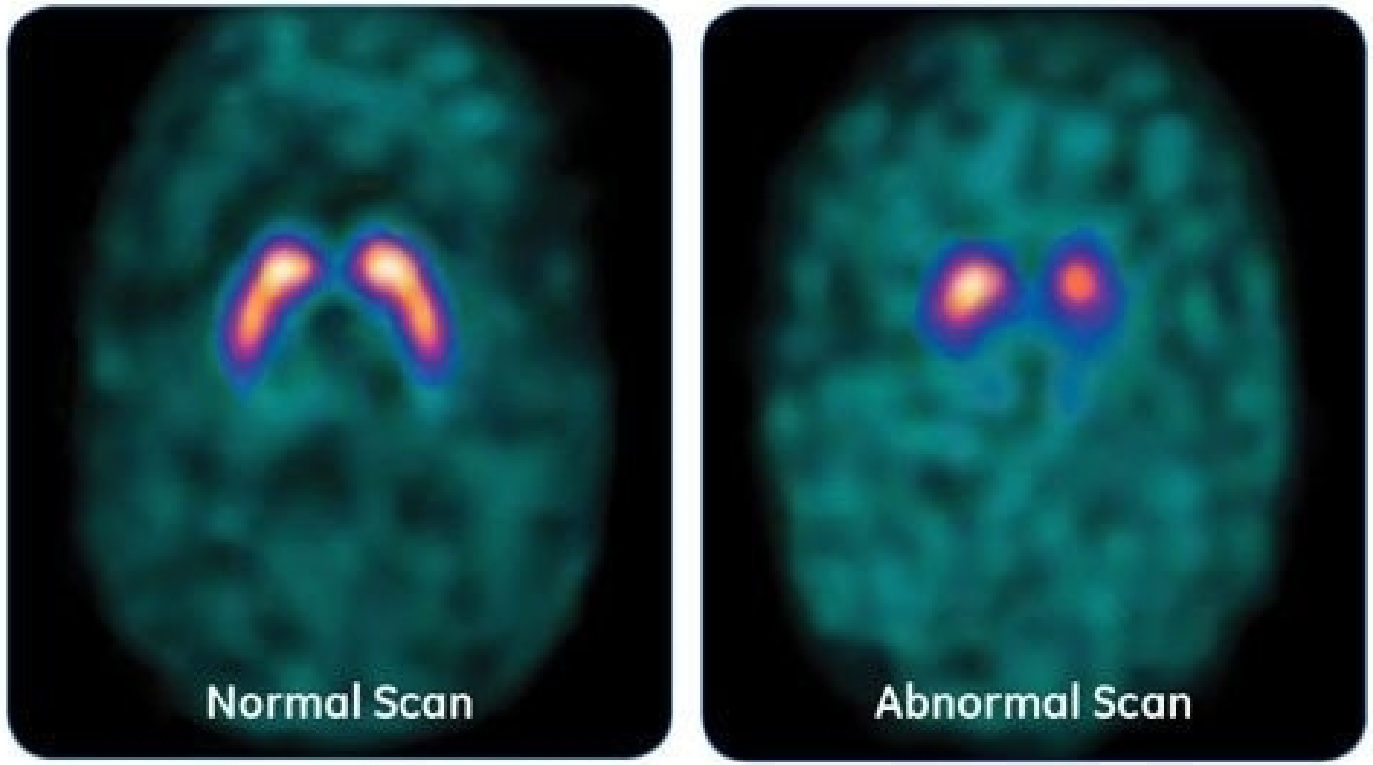
Parkinson's Disease

- Family history 5%-15%
- Alcohol does not help tremor
- Rest tremor
- Onset is unilateral
- Will have bradykinesia, others
- Tremor when walking
- Positive DaTscan



Differential Diagnosis of Essential Tremor

Stephen G Reich, Med Clin N Am 103 (2019) 351–356



"Comma"-shaped
Possible essential tremor

"Period"-shaped
Possible parkinsonian syndrome

DaTscan – SPECT ioflupane I-123

Interventions for Essential Tremor

- Education and reassurance may be sufficient for mild cases without significant functional impairment
- Best-evidence level A: propranolol and primidone (other beta-blockers have less evidence)
- Level B gabapentin, topiramate, and alprazolam
- Level C clonazepam, nimodipine, and limb injections of botulinum toxin
- Disabling tremor refractory to medical therapy, consider deep brain stimulation ventral intermediate nucleus of the thalamus (VIM) or focused ultrasound of VIM

Any Questions?

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