Movement Disorders: Diagnosis and Treatment

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Movement Disorders: Classification

HYPERKINETIC
- Tremors
- Chorea
- Tics
- Hemiballism
- Dystonia
- Myoclonus
- Restless Legs
- Paroxysmal Disorders

HYPOKINETIC
- Parkinson’s disease
- Lewy body dementia
- PSP
- MSA
- CBGD

-Parkinson's is always treatable! No matter how late stage it is.
Hyperkinetic Disorders: Essential/Familial Tremor

- 5 - 12% of Population
- 5 - 12 Hz
- Postural/kinetic
- Treatment (usu. GABA enhancing)
  - Alcohol
  - Beta-blockers
  - Mysoline (primidone)
  - Klonopin (clonazepam)
  - Topamax (topirimate)
  - Thalamic deep brain stimulation (DBS)

Topamax is best drug choice for Tx.
Deep brain stimulation works much more quickly for ET (1-2wk) vs Parkinson's (months).

Hyperkinetic Disorders: Huntington’s Chorea

- Autosomal dominant/CAG repeat
  - Average repeat 40-42, Average age @ onset 40-42
- Clinical syndrome
  - Psychiatric
  - Movement disorder
  - Cognitive
- Treatment
  - Antidepressants
  - Neuroleptics and atypical antipsychotics
  - Monoamine depleting agents
  - Benzodiazepines (clonazepam)
  - Anti-epileptics for mood stabilization

@34 repeats --> permutation; 37 repeats --> chorea (100% penetrance; Sx WILL appear at some point in pt's life).
Research in this field has exploded. Pretty rare disease, but devastating. Tx nowadays are very good!
Avg lifespan is 10-15yr after Sx onset, most common cause of death is aspiration pneumo (so often given feeding tubes).
NOTE: often movement disorders are drug induced, so ask your pt if they've started new meds.
Hyperkinetic Disorders: Tourette’s Syndrome

- Autosomal dominant with variable penetrance and sex dependence
- Clinical syndrome
  - Disabling motor/vocal tics - Duration > 1 year
  - Onset before age 18 - Idiopathic
- Tics may be simple or complex (copralalia)
- Associated features
  - OCD - ADHD
- Treatment
  - Neuroleptics - Clonadine
  - Monoamine depletors - Klonopin

Hyperkinetic Disorders: Hemiballismus

- Large amplitude, choreiform movements of one side of body or one limb
- Subthalamic nucleus infarction (classic – but may involve thalamus, basal ganglia, other sites)
- Usually self-limited
- Treatment
  - Neuroleptics
  - Monoamine depletors

-If you infarct subthalamic nucleus, thalamus becomes overactive --> wild flailing on contralateral side of body.
-Infarcts totally contained w/in STN are rare but more amenable to Tx.
-If it spreads to thalamus or basal ganglia, they can be more prolonged Sx and refractory to Tx.
-Monoamine depleting agents pretty effective at treating Hemiballismus.

-Most impt criteria: can never Dx Tourette's when pt is on a stimulant (eg, child medicated for ADHD).
-1/3 of kids grow out of it, 1/3 unchanged, 1/3 progress slowly.
-Central-acting alpha-adrenergic agonists (eg, clonadine) preferable over neuroleptics (DA blocking agents).
-B/c long-term neuroleptic use can lead to tardive dyskinesia.
-NOTE: Elmer's questions will be clinical; not on pathways.
Hyperkinetic Disorders: Dystonia

- Involuntary contraction
- Types: Focal, segmental, action, task-specific, generalized
- Causes: Primary (genetic), degenerative, post-injury, toxic, occupational, etc.
- Treatment
  - Anti-cholinergics
  - Baclofen, central alpha-adrenergic agonist
  - Botulinum toxin

Hyperkinetic Disorders: Myoclonus

- Lightning-like interruption in normal muscle activity
- Positive and/or negative
- Types: Focal, multifocal, action, reflex, generalized
- Causes: Physiologic, primary, epileptic, degenerative, post-anoxic, toxic, etc.
- Treatment
  - Klonopin (clonazepam) - Depakote (valproic acid)
  - Mysoline (primidone) - Keppra (levetiracetam)

-Dystonias are common... botox is the "breakthrough Tx"

-Often mistaken for tremor, but it's pseudorhythmical vs. tremors that are rhythmical.
Hyperkinetic Disorders: Restless Legs

• Characterized by an almost irresistible urge to move, usually associated with disagreeable leg sensations, worse during inactivity, and often interfering with sleep.
• Frequently accompanied by Periodic Leg Movements of Sleep (PLMS)
• Possibly affects 5-15% of population
• Competing theories – dopamine insensitivity versus iron deficiency

Hyperkinetic Disorders: Restless Legs

• Creepy, crawly, tingly
• Like worms or bugs crawling under the skin
• Painful, burning, or achy
• Like water running over the skin
• Sometimes indescribable

-Treatable; common; often drug induced…
Secondary Causes

- Iron-deficiency anemia
- Uremia (20-40% of dialysis patients)
- Pregnancy (up to 27%)
- Neurological lesions
  - both spinal cord and peripheral nerve lesions
- Drug-induced
  - tricyclics, SSRI’s, lithium, dopamine blockers (e.g., neuroleptics), xanthines, withdrawal from dopaminergic agents

Hyperkinetic Disorders: Restless Legs: Treatment

- Benzodiazepines
- Narcotics
- Dopamine agonists
Hyperkinetic Disorders: Paroxysmal Dyskinesias

- Kinesigenic and non-kinesigenic (PKD and PnonKD)
- May be inherited
- Secondary causes: Vascular, metabolic, inflammatory, infectious, post-traumatic, etc.
- May be exertion related – paroxysmal exercise-related dyskinesia (PED)

Parkinsonian Syndromes

- CBGD
- PSP
- SND
- SDS
- OPCA
- PD
- PDD
- DLB

-Parkinson's: *Slowness/decreased movements (40-50% of pt's don't have tremor at CP; 10-15% never have tremor).
- Often have autonomic involvement
- Amyloidopathies could be included here (Alzheimer's); can present with Parkinsonian Sx.
- Multiple System Atrophies: intracellular alpha-synuclein inclusion bodies in GLIAL cells.
- Alpha-synuclein is primary component of Lewy body NEURAL inclusions (pathological hallmark of Parkinson's).
Classification of Parkinson Syndromes in a Community

- Idiopathic PD (includes DLBD?) 85-90% of all PS cases
- Vascular parkinson’s syndrome ~ 3%
- Drug-induced parkinsonism (DIP) 1% - 3%
- MSA (SDS, SND, OPCD) ~ 2.5%
- PSP ~ 1.5%
- CBGD ~ 0.5% (?)

Parkinsonism: Increased Mortality

- Untreated IPD – average life span 7 – 9 years
- Treated IPD – average life span 15 – 20 years
- Parkinson’s Plus Syndrome – average life span of 7 – 9 years

-Treated Parkinsons now does not really decrease lifespan anymore.
68 y/o male, B.A. in business
10 years diagnosed as “Parkinson’s disease”
Multiple hallucinations and delusions
History of fluctuations – mentally and physically
Never diagnosed with “dementia”

Mini-mental status score = 16

Parkinsonism:
Dementia with Lewy Bodies

- Parkinson’s symptoms
- Other clinical features
  - Dementia - Psychosis
  - Syncope - Fluctuations
  - Myoclonus - Autonomic changes
- Treatment
  - Low dose carbidopa/levodopa
  - Atypical antipsychotics
  - Cholinesterase inhibitors
  - NMDA antagonists – memantine (?)

"Dementia with Lewy Bodies" vs. "Parkinsons dementia" is a question of timing.
-DLB: Lewy bodies scattered throughout the cortex; seem to develop at the same time.
-Parkinsons: Lewy bodies start in periphery (olfactory bulb & enteric NS.. spreads via dorsal motor nucleus of vagus into medulla; gradually works up brain stem finally to substantia nigra).
Drug Induced Parkinsonism

- Conventional Neuroleptics
- Atypical Neuroleptics
  - Risperdal (risperadone)
  - Zyprexa (olanzapine)
  - Geodon (ziprasidone)
- Anti-emetics/Gastric motility agents
  - Reglan (metaclopramide)
- Anti-convulsants
  - Depakote (valproic acid)
- Anti-arrhythmics
  - Cordarone (amiodarone)

Movement Disorders and Aging

Vascular Parkinsonism

- Abrupt onset, usually unilateral
- Step-wise or no progression
- Other signs—hemiparesis, aphasia, hyperreflexia
- Infarcts on neuroimaging helpful in confirming diagnosis

Movement Disorders and Aging

-Beware of drug induced Parkinsons!

-Basically stroke.
Atypical Parkinsonism: Clinical Features

- Early gait and balance problems
- Early onset of, or rapidly progressing, dementia
- Onset typically in 5th or 6th decade of life
- Rapidly progressive course
- Supranuclear gaze palsy
- Upper motor neuron signs
- Cerebellar signs—dysmetria, ataxia
- Urinary incontinence
- Early symptomatic postural hypotension
- Poor response to dopaminergic medications

Normal Basal Ganglia Functional Anatomy
-Net result: excessive inhibition of the thalamus (cannot initiate or maintain movement).
Multiple System Atrophy - C: Olivopontocerebellar Atrophy

- Parkinsonism
- Gait Ataxia
- Ataxic Dysarthria
- Limb Ataxia
- Sustained gaze-evoked nystagmus or other eye movement abnormalities

Multiple System Atrophy - A: Shy-Drager Syndrome

- Parkinsonism
- Autonomic failure
  - 30 mm Hg orthostatic drop in SBP
  - 15 mm Hg orthostatic drop in DBP
- Urinary/sexual dysfunction
  - persistent, involutary partial or total bladder emptying
  - erectile dysfunction in males
- Other
  - impaired sweating, constipation, iris atrophy

-Parkinson's + a ton of ataxia. Midline cerebellar Sx. Slurred speech.
Multiple System Atrophy - P: Striatonigral Degeneration

- Bradykinesia
- Rigidity
- Postural instability
- Tremor (postural, resting, or both)
- Poor or no responsiveness to levodopa

Movement Disorders and Aging

Treatment of MSA

Midodrine (blood pressure)
Sinemet (bradykinesia)
Dopaminergic Agonists (bradykinesia)
Anticholinergics (bladder, bradykinesia)
Fludrocortisone (blood pressure)

Movement Disorders and Aging

- MSA-P is the worst one. Eventually they become essentially locked-in syndrome - cognitively they are often intact :( - 5yr lifespan after Dx.
Parkinsonism: Progressive Supranuclear Palsy

- Parkinsonism
- Onset after 40, progressive
- Supranuclear gaze palsy
- Other
  - Dysarthria/dysphagia
  - Falling early

Movement Disorders and Aging

Hypokinetic Disorders: Corticobasal Ganglionic Degeneration

- Parkinsonism
- Cortical signs
  - Dyspraxia
  - Cortical sensory loss
- Dystonia
- Irregular action/postural tremor
- Myoclonus
- Alien limb

Movement Disorders and Aging

- Profound gait/balance disturbance... profound dysarthria. More cognitive/frontal problems than other diseases. Bad disease.
- 5yr lifespan after Dx.

- If you see someone who presents young or with rapidly progressing Sx like these two slides, or are refractory to meds, then refer to movement disorder specialist!!!!!!!

- Cortex all the way down to basal ganglia involved.
- Alien limb = semi-involuntary movements like stealing someone's food next to you.
- More jerky myoclonic movements than resting tremor seen in Parkinson's (both are Tau-opathies though).
Conclusions:
Parkinson’s Plus Syndromes

- Difficult to distinguish from idiopathic Parkinson’s Disease *early*
- Various neuropathophysiologic and clinical features
- Absence of satisfactory symptomatic and neuroprotective therapies – *at this time*

Hypokinetic Movement Disorders

Parkinson’s Disease: A Revolution in Management
Clinical Features/Cardinal Signs

- 1817: James Parkinson “An Essay on the Shaking Palsy”
- UK Brain Bank Criteria – Bradykinesia plus 1 of 3:
  - Rigidity
  - Tremor (primarily at rest)
  - Late (usually): Postural instability
- Onset: Insidious, unilateral progressing to bilateral

- When looking for alpha-synuclein inclusions, they start in gut (enteric NS), then olfactory bulb, then medulla.
- Autonomic disturbances like constipation; lack of sense of smell; and acting out dreams in REM sleep.
- These 3 functions are affected 10-20 YEARS before substantia nigra is affected!!! (ie, stage 4)
- Thus we can hopefully detect Parkinsons before it even occurs.
Revolutionary PD Pathology


Sites of Action of PD Drugs: 1960’s

Substantia Nigra

levodopa

DA GABA

Striatum Anti-cholinergics
Sites of Action of PD Drugs: 1990

- MAO-B
- GABA
- DA
- levodopa
- Amantadine
- selegiline
- Dopamine agonists (bromocriptine, pergolide)
- Anti-cholinergics
- BBB
- carbidopa
- benserazide

Sites of Action of PD Drugs: 2000

- MAO-B
- GABA
- DA
- levodopa
- Amantadine
- selegiline
- Dopamine agonists (bromocriptine, pergolide, pramipexole, ropinirole)
- Anti-cholinergics
- BBB
- carbidopa
- benserazide
- tolcapone
- entacapone
- baclofen

Movement Disorders and Aging
Long-term use of levodopa may be associated with motor complications

Adapted from Waters Figure 3, reprinted from Stern, 1993.
Case Study: Advanced Therapy in PD

- 51 y/o female
- Diagnosed with idiopathic PD in mid 30’s
- Treated with carbidopa/levodopa 25/250, ½ tablet q2 hours around the clock, selegiline 5 mg bid, trihexyphenidyl 2 mg tid
- Required G-tube for nutrition and medications
- Underwent fetal cell transplant in late 1990’s without benefit
- Cognitively intact

Case Study: Management of Advanced PD

- Two hospitalizations
- Removal of G-tube
- Final Medication Regimen
  - carbidopa-levodopa sustained-release 50/200 ½ tab q3 hours 6a – 9p
  - carbidopa-levodopa immediate-release 25/100 ½ tab q6a
  - tolcapone 100 mg q6a, 12 noon, 6p
  - pramipexole 0.5 mg q3 hours 6a – 9p
  - amantadine 100 mg q6a, 12 noon, 6p
  - selegiline 5 mg q6a
Goals of Current Therapeutic Strategies

Surgical Options in Parkinson’s Disease

- Pallidotomy
- Subthalamic Nucleus DBS
- Globus Pallidus DBS

-Deep brain stimulation of basal ganglia results in great improvement of Sx.
-Also physical therapy w/o any change in meds or surgery can result in huge improvements!
Percentage of Waking Time On, Off and On With Dyskinesia after Bilateral Subthalamic Stimulation As Measured By Patient Diaries

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Six Months</th>
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<tbody>
<tr>
<td>27% ON w/dysk</td>
<td>19% OFF</td>
</tr>
<tr>
<td>23% ON w/dysk</td>
<td>19% OFF</td>
</tr>
<tr>
<td>50% OFF</td>
<td>74% ON</td>
</tr>
</tbody>
</table>

All P values < 0.001

Sites of Action of PD Drugs: Emerging

- **Dopamine agonists**
- Controlled-release
- Novel DA’s
- Nasal sprays
- Other transdermal

- **Adenosine Antagonists**
- AMPA Antagonists
- Adrenergic Antagonists

**Substantia Nigra**
- DA
- Serotonergic Antagonists

**Striatum**
- GABA
- ACh
- Extended levodopa delivery systems

**MAO-B**
Conclusions

**Parkinson’s Disease:**

- **May** be diagnosed *before* motor symptoms develop
- Involves the entire nervous system – therefore, neuroprotective strategies must take this into account
- Management of motor and non-motor complications is variably effective due to human diversity

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Movement Disorders: Diagnosis and Treatment

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