FOUNDATION OF UNDERSTANDING PARKINSON’S DISEASE

- DEE SILVER M.D MOVEMENT DISORDER SPECIALIST
- MEDICAL DIRECTOR -- PARKINSON ASSOCIATION OF SAN DIEGO 1980 TO PRESENT
- SCRIPPS MEMORIAL HOSPITAL, LA JOLLA CA. 1973 TO PRESENT
OUTLINE OF FOUNDATION TALK
KNOWLEDGE IS POWER

- SIGN & SYMPTOMS OF IPD
- RED FLAGS FOR APD
- DIAGNOSTIC ACCURACY
- TREATMENT
- MAKE IT HAPPEN FOR Q OF LIFE, ACTIVITIES OF DAILY LIVING, REDUCED CAREGIVER BURDEN
Conceptual Diagram of the Phases of PD

Disease Onset

Percentage Remaining Dopaminergic Neurons

Premotor Phase

Motor Phase

Time (y)

Nonmotor Symptoms
Motor Symptoms
Dopaminergic Neurons

Lewy Body

Courtesy of Kapil D. Sethi, MD.
The Braak Hypothesis: An Evolving Concept of Disease Progression and Timing

DX OF IPD—TRIO + ONE

• BRADYKINESIA—AKINESIA
• RIGIDITY
• RESTING TREMOR
  ASYMMERTY
  – POSTURAL INSTABILITY-- LATER
  • NO KNOWN MARKER—YET
  • PROBABLY WILL NEED MORE THAN ONE MARKER BECAUSE OF THE HETEROGENEITY OF IPD
S & S OF ADVANCED IPD

▪ RESTING TREMOR
▪ AKINESIA
▪ RIGIDITY
▪ POSTURAL INSTABILITY, FREEZING GAIT
▪ DYSKINESIAS; PEAK & DIPHASIC
▪ WEARING OFF (END DOSE FAILURE-EDF)
▪ DELAYED ON & NEVER ON
▪ SPEECH & SWALLOWING DSYFUNCTION
▪ BEHAVIOR & COGNITIVE DECLINE
RED FLAGS FOR APD

- Early falling, as postural instability
- Without robust response to L-Dopa or waning effect; taper off
- Dysphagia, dysarthria, lack of asymmetry
- Early cognitive loss
- Early orthostatic hypotension
- Early Neurogenic bladder
- Neuropsych and behavior changes
- Antiflexion, Retroflexion
SNCA-alpha synuclein prone to aggregate
LRRKS-leucine-rich repeat kinase-2
GBA-beta-glucocerebrosidase
DNAJCl3, Parkin, PINK
Others, CHCHD2, VPS35, ATP13A2, C9ORF72, SCA2, SCA3, FBX07, MAPT (tau)
Etiology of PD

• Specific causative factor unknown, but genetic and environmental factors probably involved

• Rare families with inheritance of abnormal genes

• Major epidemiologic study suggests:
  – Genetic factors play larger role in young-onset patients
  – Environmental insults play larger role in patients with onset after age 50
  – Age major risk factor
RISK FACTORS

• AGE
• GENETICS
• ENVIRONMENTAL
  – HERBISIDES
  – PESTISIDES
  – RURAL LIVING
New Therapeutic Approaches Based on Trans-cellular Propagation of Protein Misfolding

- Increase microglial clearance
- Increase degradation of aggregates e.g., by lysosomes
- Inhibit protein assembly (e.g., nanomaterials)

Block release

Block uptake

Revised from Frost and Diamond 2010 (immunization)
ANTICIPATION OF IPD

- Hyposmia-85%
- RBD-alpha synuclein syndromes – IPD, LBD, MSA—early predictor, as much as 15 yrs, 85%
- Depression
- Constipation-30 to 50%
## Non-motor Symptoms

<table>
<thead>
<tr>
<th>Cognitive/Psychiatric</th>
<th>Autonomic</th>
<th>Sensory/Pain</th>
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</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Drenching sweats</td>
<td>Tingling sensation</td>
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<tr>
<td>Depression</td>
<td>Dyspnea</td>
<td>Akathisia</td>
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<tr>
<td>Fatigue</td>
<td>Orthostatic hypotension</td>
<td>Olfactory deficit</td>
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<tr>
<td>Slow thinking</td>
<td>Sexual dysfunction</td>
<td>Diffuse pain</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Seborrhea</td>
<td>Back &amp; shoulder</td>
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<tr>
<td>Sleep dysfunction*</td>
<td>Constipation</td>
<td>Hot-cold sensations</td>
</tr>
<tr>
<td>Sleep fragmentation</td>
<td>Urinary urgency</td>
<td>Burning</td>
</tr>
<tr>
<td>RBD &amp; OSA</td>
<td>Neuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RLS</td>
<td></td>
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<tr>
<td></td>
<td>Melanoma</td>
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</table>
ACCURACY OF DIAGNOSIS COMPARED WITH AUTOPSY

- London Brain Bank—75% at initial exam; and 90 to 95% final diagnosis
- Mayo—At 5 years into care, 50% and at final diagnosis 80 to 85%
- Reports of patients with MSA, PSP, CBS; diagnosis only 60% correct with autopsy
Dopamine Transporter Imaging in PD

Healthy subject

PD patient – Hoehn-Yahr Stage 1
DaTscan™ (Ioflupane I 123 Injection) SPECT Images

Normal Uptake, No Dopaminergic Deficit

Consistent with:
Essential Tremor

3 Patients With Abnormal Uptake, Dopaminergic Deficit

Consistent with:
Parkinson’s Disease
Multiple System Atrophy
Progressive Supranuclear Palsy

MRI AND THE SWALLOW TAIL

- 3 TESLA MRI
- NeuroQuant analysis-volumetric
- Absence of the Swallow Tail sign
- Absent high signal within the posterior third of the substantia nigra
- Indicates loss of dopamine neurons.
- Correlates clinically at about 85%
Algorithm for the Treatment of Early Parkinson’s Disease

SIDE EFFECTS OF DA

- Drowsiness, sleepiness, fatigue
- Sudden sleep events
- Nausea
- Orthostatic hypotension, new or worsening
- Confusion, hallucinations, delusions,
- Ankle swelling,
- Red and swollen hands
- Compulsive, impulsive disorders (ICD), ie gambling, pornography etc.
- Possible fibrosis
L-DOPA RX MOST ROBUST THERAPY BUT FREQUENT MOTOR COMPLICATIONS- 2 TYPES-

- Wearing-off; End dose failure, Morning off
  - Delayed on, Never on

Drug-induced dyskinesias
  - Peak dyskinesias
  - Diphasic dyskinesias

Dystonias- On & Off

AM & HS Dystonia
Disease-Related Symptom Evolution Despite Optimal Levodopa Therapy

- Postural imbalance, freezing
- Dysarthria, dysphagia
- Nonmotor symptoms-Cognition
- Neuropsych symptoms
- Comorbidity (45% at autopsy have DAT)

MANAGEMENT OF BEHAVIOR DISORDERS

- SSRI’S
- SNRI’S
- TRICYLICS
- Quetiapine (Seroquel)
- Pimavanserin (Nuplazid); first drug released for hallucinations and delusions.
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