Objectives

- Describe the scope of the Neurodegenerative disorders
- Review the Classification of the Neurodegenerative disorders
- Discuss the similarities and differences within the various Neurodegenerative disorders
- Discuss the palliative management of patients with Neurodegenerative Diseases
Establish the scope of need for Palliative care as applied to persons with chronic debilitating neurological diseases, and to the practice of neurology
- Magnitude of the problem
- Glimpse into Neurologist’s world

Review the Diagnosis and Pathophysiology of the movement disorders
Reacquaint the key Differential Diagnoses of the movement disorders
Review current pharmacologic treatments
Understand the clinical course of PD and its correlates
Foci

- Incorporate a comprehensive palliative approach to pts with advanced Neurodegenerative disorders, especially PD and its correlates
  - Attention to both movement related and non-movement related manifestations

Introduction

Progressive neurodegenerative disorders are common, partially understood, and poorly addressed in palliative care. Profound effect on Life Quality and Function. NO Curative Options.

- Prevalence progresses markedly w age
  - 1-2% of people >65
  - 2.6% >85
  - 50%+ >85 w Parkinsonism
  - Over 1 million US citizens
  - PD is the second most common neurodegenerative dz.
  - 5.2% in LTC

- Life expectancy of persons w PD only slightly < average in gen’l
- Life expectancy of the Other Neurodegenerative Disorders much less
Introduction

“The relationship of the patient to Death is not by any means the same thing as the medical probability of recovery”

-Robertson Davies, 1994

The Historical Classifications

Alzheimer's Disease
Frontotemporal Dementia
Huntington's Disease
Spinocerebellar Ataxias
Friedreich's Ataxia
Parkinson's Diseases
Other Parkinsonian Syndromes
  PSP-Prg Supranuclear Palsy
  MSA-Multisystem Atrophy
  OPCD-Olivopontocerebellar Degen.
  SNDF-Striatonigral Degen.
  S-DS-Shy-Drager Syndrome
Diffuse Lewy Body Dz
Others

Metal Storage Disorders
  Wilson’s Dz
  Iron Storage Disorders
Other Neurologic Disorders
  Amyotrophic Lateral Sclerosis
  Other Motor-Neurone Disorders:
    Progressive Muscular Atrophy
Spinal and Bulbar Muscular Atrophy [Bulbar & Pseudobulbar Palsey’s]
Familial Spastic Paraparesis
Primary Lateral Sclerosis
# The Classifications-By Movements

<table>
<thead>
<tr>
<th>Hyperkinetic Disorders</th>
<th>Hypokinetic Disorders</th>
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<tbody>
<tr>
<td>Tremors</td>
<td>Bradykinesia</td>
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<tr>
<td>Chorea</td>
<td>Rigidity</td>
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<tr>
<td>Ballism</td>
<td>Postural Disturbances</td>
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<tr>
<td>Dystonia</td>
<td>Parkinsonian Syndromes</td>
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<tr>
<td>Athetosis</td>
<td>Idiopathic Parkinsonism (IP)/</td>
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<tr>
<td>Athetosis</td>
<td>Parkinson’s Dz</td>
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<tr>
<td>Myoclonus</td>
<td>Progresssive Supranuclear</td>
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<tr>
<td>Tics</td>
<td>Palsy</td>
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<tr>
<td>Stereoty</td>
<td>Multisystem Atrophy</td>
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<tr>
<td>Akathisia</td>
<td>Corticobasal Ganglionic</td>
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<tr>
<td>Periodic Leg Movement in Sleep</td>
<td>Degeneration</td>
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<tr>
<td>Restless Leg Syndrome</td>
<td>Dementia with Lewy Bodies</td>
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<tr>
<td>The Dyskinesias</td>
<td>Frontotemporal Dementias</td>
</tr>
<tr>
<td>Startle Dz or Hyperekplexia</td>
<td>with Parkinsonism</td>
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<tr>
<td>Alien Limb</td>
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<tr>
<td>Hemifacial Spasm</td>
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<tr>
<td>Stiff Person Syndrome</td>
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# Towards a Changed Classification System


**June 24, 1999 Number 25**

“Molecular Basis of the Neurodegenerative Disorders”

Joseph B. Martin, M.D., Ph.D.
Classification-Molecular Basis

Neurodegenerative disorders, which are chronic and progressive, are characterized by selective and symmetric loss of neurons in motor, sensory, or cognitive systems. Delineation of the patterns of cell loss and the identification of disease-specific cellular markers have aided in nosologic classification: senile plaques, neurofibrillary tangles, neuronal loss, and acetylcholine deficiency define Alzheimer's disease; Lewy bodies and depletion of dopamine characterize Parkinson's disease; cellular inclusions and swollen motor axons are found in amyotrophic lateral sclerosis; and -aminobutyric acid–containing neurons of the neostriatum are lost in Huntington's disease. Mendelian inheritance can be demonstrated in some.

Pathophysiology

Parkinson’s

- Multiplicity of presentations and cell type deterioration, in addition to:
  - Primary dopamine deficiency from predominantly nigro-striatal pathways
    - Disruption of communication btw the BG, Thalamus, Cortex
  - Increasing ambiguity as to the historical attributes of PD
Pathophysiology

- Defining PD now more difficult: recognition of heterogeneous syndrome
- Etiology unknown
  - Speculation as to combination of genetic predisposition and toxins
    - 11 or so defined assoc. genes
    - Prior illness, diet, rural, well water, pesticide exposure, trauma implicated
- Lewy Bodies present in histologic foci = gold standard of dx

Pathophysiology

- Latency period from anatomic brain changes to clinical symptoms ~5yrs
- Sx’s evident at ~80% neuronal loss
- Additive effect of normal age related neuronal loss
- Progression of disease unaltered by current tx and generally 10-20 year course
Clinical Symptoms

- Derivation of Original per Dr. Parkinson, Paralysis Agitans=Shaking Palsy
  - Could apply to several different movement disorders known today
- Triad: Tremor, Rigidity, Bradykinesia
  - Plus inclusion/exclusion criteria = definition of Idiopathic Parkinsonism*
    - (IP)=75% Parkinsonism cases

Differential Diagnosis - PD: Atypical Parkinson Syndromes

- Essential tremor - [most common M D]
- Drug-Induced Parkinsonism
  - Neuroleptics, Meperidine, DA antagonists:
    - Haloperidol, metoclopramide, DA depletors: reserpine, tetrabenazine
  - Others reported
- Vascular parkinsonism
  - Multiple BG infarts
- Progressive Supranuclear Palsy
- Cortico-Basal Ganglionic Degeneration
Differential Diagnosis - PD: Atypical Parkinson Syndromes

- Parkinsonism with Cerebellar and Autonomic Dysfunction: The Multiple System Atrophies (MSA)
  - Striatonigral Degeneration (SND)
  - Shy-Drager Syndrome (SDS)
    - Progressive pandysautonomia
    - symmetrical
  - Olivoponocerebellar Atrophy (OPCA)
    - Progressive cerebellar ataxia

Differential Diagnosis - PD: Others

- Hereditary/Metabolic Parkinsonism:
  - Wilson’s Disease
  - Juvenile Huntington’s Disease
  - Machado-Joseph Disease
  - Hallervorden-Spatz Disease
  - Iron Storage Disorders
Clinical Symptoms: IP

- Inclusion/Exclusion Criteria:
  - No detectable cause
  - Therapeutic response to DA
  - No cerebellar findings
  - Pyramidal features limited to +/- ^ Reflexia & extensor plantar response
  - No LMN findings
  - No EOM findings x upward
  - Autonomic deficits are minor early on
  - No severe early dementia

Clinical Motor Symptoms: IP

- Rigidity: Stiffness, Cogwheeling. Often Asymmetric, Progress to “flexed posture”.
- Abn. Posture, Gait, Balance
  - “Pull test”
  - Progression to short, narrow, shuffling
- Bradykinesia: [Most disabling]. Slow volition + poverty of NI Assoc. movements. DA -dependent. ADL’s.
  - Arm swing, buttoning/tying, hand-grasp opening/closing, transferring, turning, micrographia, Hypophonia.
- UPDRS = Rating scale for assessing [bradykinesia].
  - 7 points
  - Purdue Peg board
  - Hoehn & Yahr scale
  - 5 stages
Clinical Nonmotor Symptoms: IP

- Craniofacial
- Cognitive
- Autonomic
- Sensory
- Musculoskeletal
- Dermal
- Psychiatric
- Other

Note: Secondary features progressive; key areas for palliation.

Craniofacial:
- Excess Salivation
- Masked facies
- Decrease blinking
- Olfactory hypofn.
- Dysarthria
- Blurred vision

Cognitive: 7-85% (20%)
- Dementia: cortical & “subcortical”
- Bradyphrenia
- Visuospatial, attention, & executive deficits

Autonomic:
- Orthostasis
- Poor GI Motility
- Upper & lower
- Urinary dysfn.
- Thermoregulation
- Impotence
- Excess sweating
  Sialorrhea
Clinical Nonmotor Symptoms: IP

- **NeuroSensory:**
  - Paraesthesias
  - Pain
  - Dysaesthesias

- **Musculoskeletal:**
  - Cramps
  - Scoliosis
  - Wrist/foot dystonia
  - Edema

- **Dermal:**
  - Seborrhea
  - Late = Decubiti

- **Psychiatric:**
  - Depression
  - Anxiety
  - Sleep Disturb >65%
    - Hypnosis, somnolence, dreams, RLS, PLMD, Sleep Apnea
  - Sexual Dysfn.

- **Other:**
  - Weight loss
  - Anorexia

**Psychiatric: 4-70% reported incidence**
- Depression: 40-50% at some time, 31% at any given time.
- Anxiety: 25-40% prevalence.
  - Multiple overlapping sx’s
- Psychosis: 15-40%.
  - Delusions, disruption, paranoia, hallucinations, phobias, apathy
  - Potential SE of Rx as well
- Higher incidence in post surgical pts.
Clinical Nonmotor Symptoms: IP

- Pain: common in PD
  - 20-50% at any given time, {46%}
  - Most closely w poor motor fn.; next w dystonia and chorea
  - Also assoc w sensory dysfn.
    - Multiple and diffuse, thought central origin
    - Oral & Genital Pain syndromes - unique, & +/- atypical for neurogenic (varied)

Differential Diagnosis:
Atypical Parkinson Syndromes

- Disorders with Dementia as Primary or Early Manifestation
  - Diffuse Lewy Body Disease
  - ATD with Parkinsonism
  - Parkinsonism-Dementia Complex of Guam
  - Normal Pressure Hydrocephalus
  - Crutzfeldt-Jacob Disease
  - Pallidopontonigral degeneration & DDPAC
  - Early Onset Parkinsonism
  - Dopa-responsive Dystonia
  - Hemiparkinsonism-Hemiatrophy Syndrome
  - Toxin-Induced Parkinsonism
    - *Manganese
    - *MPTP
Differential Diagnosis:
Key Features

- Virtually all pts w IP will respond favorably to DA-mimetic Rx
- Others that will respond, are transient or partial
- Avg age onset mid 6th decade
- Usually asymmetric earlier
- NO absolute dx tests
- Think other causes if:
  - Early dysautonomia, rapid dementia, cerebellar sx’s, ocular dysfn. Focal neuro deficits, poor response to l-dopa
- IP slowly and variably deteriorates

Pharmacotherapy-PD

- **Anticholinergics:**
  - Cogentin
  - Akineton
  - Artane,Trihexyl
  - Diphenhydramine

- **Antiviral:**
  - Amantadine

- **Dopaminergic:**
  - L-dopa / CR/ combo

- **DA Agonists/Ergot:**
  - Bromocriptine
  - Pergolide
  - Cabergoline
  - Lisuride

- **DA Ag./Non-Ergot:**
  - Apomorphine
  - Pramipexole
  - Ropinirole
Pharmacotherapy - PD

- COMT Inhibitor:
  - Entacapone
  - Tolcapone
- MAO-B inhibitor:
  - Selegiline
  - Rasagiline

In Phase III Testing:

- Selegiline s.l.
- Rivastigmine (Exelon)
  - AcCh Inhib.
- Rotigotine patch
  - DA Ag/non-ergot

Surgical Therapy - PD
[Not for late stage disease]

- Thalamotomy
  - Tx tremor
- Pallidotomy
  - Tx cardinal motor signs
- Deep Brain Stimulation
  - Preferred Method
  - Safer and more effective in gen’l
  - Consideration as combination w cut
Managing Advanced Disease - PD

With progression, response to L-dopa less, and more variable; motor complications develop. Tx is very tedious and individualized, attentive to narrower therapeutic window of L-dopa & almost always w COMT Inhib as part of regimen, as is dose fractionation (lower doses given more frequently). Also frequently used is “full team Rx in lowered doses. Adverse drug rxns more common. Polypharmacy concerns w co-morbid tx as well as tx for secondary sx’s. >Pain & Sx Mgmt ^^^.

Managing Advanced Disease - PD

Appreciate the unique phenomenon of “wearing off” in treating PD
Understand different treatment options for dealing with some complications in late term treatment of PD
Managing End Stage Disease

- When pts are bed bound, often many of Rx are discontinued.
- MUST attend to secondary manifestations.
- Hospice referrals optimal, of course.
- Practice Non-Abandonment and Support
  - Social and Financial Isolation are often Huge problems
  - Caregiver burnout a concern

James Parkinson’s Description

As...the influence of the will over the muscles fades, the tremulous agitation becomes more vehement...The motion becomes so violent as not only to shake the bed hangings, but even the floor and sashes of the room. The chin is now almost immovably bent down upon the sternum. The slops with which he is attempted to be fed, with the saliva, are continually trickling from the mouth. The power of articulation is lost. The urine and faeces are passed involuntarily, and at the last, constant sleepiness announce the wished-for release.
Commonalities Among the Lot

- Neurobehavioral Disorders
  - Neuropsychiatric
  - Cognitive
  - Dementing
- Musculoskeletal symptoms
- Neuromuscular symptoms
- Autonomic symptoms

Commonalities Among the Lot

- Neuropsychiatric Disturbances:
  - Depression >60%
  - Mania
  - Psychoses
  - Personality Changes
  - Obsessive-Compulsive DO
  - Anxiety >75%
  - Sleep DO
  - Sexual DO
Commonalities Among the Lot

- Cognitive Disturbances
  - Executive Functioning
  - Memory Deficits
  - Speech & Language Dysfunction
  - Visuospatial Functioning
  - Praxis

Common Rx in General Tx

- Tx Spasticity
  - Stretching & Exercise
  - Baclofen start 10mg q day
  - Tizanidine start 4mg q day

- Tx Cramps
  - Quinine 650 mg at hs
  - Benzodiazepines

- Tx Focal Dystonia
  - Botulinum toxin A
**Common Rx in General Tx**

- **Tx Excess Oral Secretions**
  - Glycopyrrholate 1-2 mg tid
  - Anticholinergic
  - Tricyclics
  - Scopolamine
  - Atropine

- **Tx Orthostasis**
  - Stockings
  - HOB elevated at night
  - Increased salt intake
  - Rx Fludrocortisone 0.1-.3 mg/day
  - Rx Ephedrine 15-45 mg tid
  - Rx L-threo-DOPS 300 mg bid
  - Rx Midodrine 2.5-10 mg tid
### Common Rx in General Tx

- **Tx Post-Prandial Hypotension**
  - Octreotiide 25-50 mcg sq ac

- **Tx Nocturnal Polyuria**
  - Desmopressin
    - Spray 10-40 mcg q hs
    - Tablets 100-400 mcg q hs

- **Tx Bladder Symptoms**
  - Catheterization, Intermittent or permanent, for retention or residual volume >100cc
  - **Tx Spasms**
    - Rx Oxybutynin 2.5-5 mg bid-tid
    - Rx Hyoscamine 0.125-0.3 qid
    - Long Acting .375 bid/tid - 0.75 bid
Common Rx in Specific Tx

- CPAP/BiPap. in MSA/ALS
- Tracheostomy/Ventilator in ALS
- Gastostomy Tubes
- Shunt Surgery in NPH
- Intrathecal baclofen for severe dystonias

Take-home messages

- Advanced Care Planning!!!
- Incorporate Goal-Directed Care Early & Often!!!
- Encourage Parkinson Support Group Participation Early
Q & A
“Death: The final effort of the patient to embarrass his physician publicly.” — Thomas & Schreiner
“Death is nature’s way of telling you to slow down.” — Sharples
“When I die I want to go peacefully like my grandfather did, in his sleep. Not screaming, like the passengers in his car.” — Michael Jeffreys
“No disease is lethal, only life is.” — Matko Marusic
“It’s a funny world—a man’s lucky if he can get out alive.” — WC Fields

Abbreviated Resources
Abbreviated Resources


Additional References

- David-chpc@COVENANTCARE.NET
- Handout