

Palliative Care & Neurodegenerative Diseases

T&NMHO/TAPM Annual
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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

Foci

- 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

Foci

- 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 □ 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	Metal Storage Disorders
Frontotemporal Dementia	Wilson's Dz
Huntington's Disease	Iron Storage Disorders
Spinocerebellar Ataxias	Other Neurologic Disorders
Friedreich's Ataxia	Amyotrophic Lateral Sclerosis
Parkinson's Diseases	Other Motor-Neurone Disorders:
Other Parkinsonian Syndromes	Progressive Muscular Atrophy
PSP-Prg Supranuclear Palsy	Spinal and Bulbar Muscular Atrophy [Bulbar & Pseudobulbar Palsey's]
MSA-Multisystem Atrophy	Familial Spastic Paraparesis
OPCD-Olivopontocerebellar Degen.	Primary Lateral Sclerosis
SND-Striatonigral Degen,	
S-DS-Shy-Drager Syndrome	
Diffuse Lewy Body Dz	
Others □	

The Classifications-By Movements

Hyperkinetic Disorders

Tremors
 Chorea
 Ballism
 Dystonia
 Athetosis
 Myoclonus
 Tics
 Stereoty
 Akathisia
 Periodic Leg Movement in Sleep
 Restless Leg Syndrome
 The Dyskinesias
 Startle Dz or Hyperekplexia
 Alien Limb
 Hemifacial Spasm
 Stiff Person Syndrome

Hypokinetic Disorders

Bradykinesia
 Rigidity
 Postural Disturbances
 Parkinsonian Syndromes
 Idiopathic Parkinsonism (IP)/
 Parkinson's Dz
 Progerssive Supranuclear
 Palsy
 Multisystem Atrophy
 Corticobasal Ganglionic
 Degeneration
 Dementia with Lewy Bodies
 Frontotemporal Dementias
 with Parkinsonism

Towards a Changed Classification System

NEJM Volume 340:1970-1980

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^{1,2}; Lewy bodies and depletion of dopamine characterize Parkinson's disease³; cellular inclusions and swollen motor axons are found in amyotrophic lateral sclerosis⁴; and -aminobutyric acid-containing neurons of the neostriatum are lost in Huntington's disease.⁵ 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
 - Olivopuncocerebellar 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

- | | |
|---|--|
| <ul style="list-style-type: none"> ■ <u>Tremor</u>: Asymmetric, Resting. Initial intermit., Progressive bilateral. ■ <u>Rigidity</u>: Stiffness, Cogwheeling. Often Asymmetric, Progress to “flexed posture”. ■ <u>Abn. Posture, Gait, Balance</u> <ul style="list-style-type: none"> – “Pull test” – Progression to short, narrow, shuffling | <ul style="list-style-type: none"> ■ <u>Bradykinesia</u>: [Most disabling]. Slow volition + poverty of NI Assoc. movements. DA -dependent. ADL's. <ul style="list-style-type: none"> – Arm swing, buttoning/tying, hand-grasp opening/closing, transferring, turning, micrographia, Hypophonia. ■ UPDRS = Rating scale for assessing [bradykinesia]. <ul style="list-style-type: none"> – 7 points – Purdue Peg board ■ Hoehn & Yahr scale <ul style="list-style-type: none"> – 5 stages |
|---|--|

Clinical Nonmotor Symptoms: IP

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

Note: Secondary features progressive; key areas for palliation.

Clinical Nonmotor Symptoms: IP

- 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

Clinical Nonmotor Symptoms: IP

- 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

- | | |
|----------------------------|-----------------------------|
| ■ <u>Anticholinergics:</u> | ■ <u>DA Agonists/Ergot:</u> |
| – Cogentin | – Bromocriptine |
| – Akineton | – Pergolide |
| – Artane, Trihexyl | – Cabergoline |
| – Diphenhydramine | – Lisuride |
| ■ <u>Antiviral:</u> | ■ <u>DA Ag./Non-Ergot:</u> |
| – Amantadine | – Apomorphine |
| ■ <u>Dopaminergic:</u> | – Pramipexole |
| – L-dopa / CR/
combo | – Ropinirole |

Pharmacotherapy -PD

- | | |
|---|---|
| <input type="checkbox"/> COMT Inhibitor: | <u>In Phase III Testing:</u> |
| <input type="checkbox"/> Entacapone | <input type="checkbox"/> Selegiline s.l. |
| <input type="checkbox"/> Tolcapone | <input type="checkbox"/> Rivastigmine (Exelon)
AcCh Inhib. |
| <input type="checkbox"/> MAO-B inhibitor: | <input type="checkbox"/> Rotigotine patch
DA Ag/non-ergot |
| <input type="checkbox"/> Selegiline | |
| <input type="checkbox"/> Rasagiline | |

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 Description¹⁸¹⁷

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

- Glycopyrrrolate 1-2 mg tid
 - Anticholinergic
- Tricyclics
- Scopolamine
- Atropine

Common Rx in General Tx

■ 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
 - Octreotide 25-50 mcg sq ac
- Tx Nocturnal Polyuria
 - Desmopressin
 - ❖ Spray 10-40 mcg q hs
 - ❖ Tablets 100-400 mcg q hs

Common Rx in General Tx

- 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 .375bid/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

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Additional References

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Handout