PARKINSON’S DEMENTIA AND RELATED CONDITIONS

Diagnosis and therapy

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Abnormal Build-up of Protein in Cells:
- Alpha-synuclein – Abnormally Folded Protein
- Garbage Disposal is overwhelmed

Classically found in “Synucleinopathies”
- Parkinson’s Disease
- Lewy Body Dementia
- Multisystem Atrophy

Ref 12 – Lewy body in the Substantia Nigra.
LEWY BODIES AND THEIR LOCATIONS

- **Location, location, location**

- Begins peripherally
  - GI
  - Skin

- Travels up the Vagus Nerve
  - Transported by axons

- Dementia - expansion to bilateral fronto/parietal lobe projections and hippocampal circuit
  - Rapid vs slow
  - Timing can often determine Diagnosis and Prognosis

Ref 14 – Lewy body locations, and amyloid plaque/neurofibrillary tangle development
DEMENTIA IN PARKINSON’S DISEASE

Motor Symptoms:
- Basal ganglia – inputs of Dopamine, Acetylcholine, Norepinephrine
- Substantia Nigra pars compacta - ~400,000 dopamine neurons
- 70% loss with initial symptoms

Memory/Cognitive Symptoms
- Eventual extension of pathology to hippocampal circuit and bi-frontal/parietal areas
- Early Mild Cognitive Impairment
- Later can have similarities with Alzheimer's
- Tau = neurofibrillary tangles in AD
LEWY BODY DEMENTIA

- Dementia with Lewy Bodies, Diffuse Lewy Body Disease

- 30% of all dementias\(^4\), second to Alzheimer’s.
  - 1.4 million people\(^6\)

- Classically associated with:
  - EARLY cognitive change (within 1 yr of PD symptoms)
  - Relatively rapid onset
  - Fluctuating cognitive impairment
  - Visual hallucinations
  - Parkinsonism
  - Sensitivity to
    - Dopamine replacement – hallucinations, side-effects
    - Neuroleptics – catatonia, rigidity

- REM Behavioral Sleep Disorder now part of diagnostic criteria\(^5\)
Pathology:
- Alzheimer’s pathology usually present on autopsy (neurofibrillary tangles/tau)
- Significant loss of:
  - Cholinergic neurons – cognitive change similar to AD
  - Dopaminergic neurons – Parkinsonian symptoms

Eventually, Parkinson’s Disease Dementia and Lewy Body Dementia are pathologically indistinguishable

Location versus Timing
PET SCAN DATA COMPARING DLB, PD, PDD

18F-flurodopa uptake
Dopaminergic system

MP4A uptake
Cholinergic uptake

FDG uptake
Glucose metabolism

Ref 2
GREY MATTER LOSS: LBD VS ALZHEIMER’S

Cortical grey matter loss

Ref 15
IMPACT ON NEUROTRANSMITTER NUCLEI

Ref 15 – Location of Grey Matter loss in Lewy Body Dementia
OTHER PARKINSONIAN SYNDROMES

- Multisystem Atrophy (MSA)
- Progressive Supranuclear Palsy (PSP)
- Corticobasal degeneration (CBD)
Cognitive impairment from a number of reasons, including:
- Initial reduction in Acetylcholine
- Later overexpression of glutamate damages cells

↑↑↑ Acetylcholine, ↓↓↓ glutamate (through NMDA)

Enhanced cognition AND reduction in hallucinations
Block breakdown of Acetylcholine → Stays around cell longer → Improves function

- **Donepezil (Aricept®)** – inhibits acetylcholinesterase
- **Rivastigmine (Exelon®)** – inhibits butyrylcholinesterase and acetylcholinesterase

Exelon is only of the two FDA approved for Parkinson’s Dementia
- Patch form, reduces risk of nausea/vomiting

Because nucleus problem and not receptor problem, patients respond better than those with Alzheimer’s\(^8\)
With LBD and PDD, acetylcholine is reduced
- Triggers an increase in glutamate to compensate for the impaired functioning.
- Overstimulation with glutamate causes neuronal hyperexcitability and death.

Memantine (Namenda®)
- Blocks glutaminergic NMDA receptors
  - Reduces glutamate activity

Corrects overexpression of glutamate

No benefit in early dementia

Structurally similar to Amantadine → reduction in dyskinesias and other PD side-effects.
Nuplazid (Pimavanserin)™

- First antipsychotic medication specifically designed for hallucinations and ‘psychosis’ associated with Parkinson’s Dementia and Lewy Body Dementia.
- Serotonin Agonist with no impact on dopamine receptors
- + SAPS-PD improvement with no change in UPDRS

HALLUCINATIONS AND PSYCHOSIS

Avoid medications that block dopamine or acetylcholine

- Neuroleptics
- Cold medication
- Anti-emetics
- Older Parkinson’s medications such as Artane
60% of Parkinson’s patients have clinical depression\(^\text{10}\)
- Equal numbers with Anxiety

- Serotonin, Norepinephrine and Dopamine all significantly reduced in Parkinson’s
  - Sleep, focus, mood, attention, etc.

- Depression, Anxiety and Fatigue missed by Neurologists up to 50% of the time\(^\text{11}\)

- Treatment with SNRI or SSRI can significantly improve cognitive function in some patients

Depression masquerading as Dementia in the Parkinson’s community.
WHAT ELSE CAN I DO?

- Activity!!
  - Physical and Mental

- Healthy Diet
  - Heart health is similar to Brain health
  - Cholesterol, blood pressure, diabetes

- No strong evidence for any particular diet or supplements
Memory, cognitive functioning and mood are directly linked to Acetylcholine and Dopamine.

- Treatment is complicated due to balance of treating motor and non-motor symptoms, incorporating different neurotransmitter circuits to give benefit without side-effects.

Proper diagnosis is key, as treatment is different

- Parkinson’s vs Lewy Body dementia vs Parkinson’s dementia vs Parkinson’s plus syndromes
- +/- Depression

Integrating a Movement Disorders Specialist into your treatment team
THANK YOU

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