The Lewy Body Dementias

Jonathan M. Beary, D.O., D.A.B.P.N.
Adjunct Assistant Professor of Neurology
Department of Neurobehavioral Sciences
A. T. Still University
Objectives

• Know the four primary clinical features of Dementia with Lewy Bodies and the corresponding treatments.
• Be able to calculate the Lewy body composite risk score.
• Understand the “one year rule” in distinguishing Dementia with Lewy Bodies from Parkinson Disease Dementia.
• Be able to distinguish Parkinson’s Disease from Parkinson mimics.
Financial Disclosures

• None Relevant to this lecture
• 63 year old male
• 10/2013: multiple *nonspecific* symptoms
  – Constipation, urinary difficulty, heartburn, insomnia, and a poor sense of smell with prominent anxiety. He also had a slight intermittent tremor in his left hand that was attributed to an old shoulder injury.
• Anxiety and fear increased.
• 12/2013: Paranoia, delusions, insomnia, memory difficulty.
• Psychotherapy and other medical help was sought.
• 4/2014: He was prescribed an antipsychotic medication which helped with anxiety but caused confusion. Patient’s wife noted he seemed to be “loosing his mind.”
• Blood work, MRI imaging were unrevealing apart from elevated cortisol levels.
• 5/2014: Diagnosed with Parkinson disease in the setting of decreased facial expression, hypophonia, left hand tremor and gait instability.
• Developed difficulty with depth perception and judging distances. Increased confusion. No hallucinations reported to his wife or doctors.
• 6/2014: pramipexole was stopped and he was started on carbidopa/L-dopa.
• Wife started sleeping in separate places from husband.
• 8/2014: Patient seemed less delusional.
• Less than one year after onset of “nonspecific symptoms”, patient committed suicide.
• Autopsy revealed 40% loss of dopamine neurons and these . . .
LEWY BODY DEMENTIA
by the numbers

1 MILL.
More than 1 million are affected by LBD

2-20
The time span of having LBD can range from 2-20 years,

5-7
but it typically lasts an average of 5-7 years from the time of diagnosis to death

50
Typically begins at age 50 or older, but sometimes younger people can have it

♂ ♂
Appears to affect slightly more men than women

80%
Visual hallucinations occur in up to 90% of people with LBD

Williams, S.S. The Terrorist Inside My Husband’s Brain
*Neurology* 2016 87(13) 1308-1311
The Lewy Body

• 1912 - Friederich Lewy described cytoplasmic inclusions in the forebrain; two years later it was linked with Parkinson disease.

• 1961 - Cortical Lewy bodies were first linked with dementia; considered rare.

• 1980s - Ubiquitin & α-synuclein immunostains revealed that Lewy bodies were common in dementia, second only to Alzheimer pathology.
Synucleinopathies

1. Parkinson Disease
2. Dementia with Lewy Bodies
3. Multiple System Atrophy

Rounded neuronal cytoplasmic inclusion containing α-synuclein

Cortical Lewy Bodies  Brainstem Lewy Bodies
Neurodegenerative Proteinopathies

Synucleinopathy
- Parkinson disease
- Dementia with Lewy bodies
- Multiple system atrophy
- Familial Parkinsonisms

TDP-43 Proteinopathy
- ALS-FTD
- FTLD-U/MND
- ALS/Parkinson disease complex of Guam

Tauopathy
- Progressive supranuclear palsy
- Corticobasal degeneration
- Frontotemporal lobar degeneration
- Alzheimer disease

Amyloidopathy
- Alzheimer disease
- Dementia with Lewy bodies
- Corticobasal Degeneration

Modified
McFarland, N.
Continuum (Minneap Minn) 2016;22(4):1117-1142.
PARKINSON DISEASE & ATYPICAL PARKINSONISM
Parkinson Disease

• Second most common neurodegenerative disease after Alzheimer disease
• Develops 5\textsuperscript{th} to 6\textsuperscript{th} Decade of life; decreased dopamine production in the \textit{substantia negra pars compacta}.
• \textbf{Tremor} – at \textit{rest}, pill rolling, MCP tremor
• \textbf{Rigidity} – cogwheeling, at elbows
• \textbf{Akinesia/bradykinesia/hypokinesia}\textsuperscript{*} - slow initiation of movements; masked facies, micrographia, hypophonia, decreased rate/amplitude of finger tapping
• \textbf{Postural instability} – stooped posture, slow, shuffled gait, block-like turning
• Respond to L-dopa

Videos: \url{Links.lww.com/CONT/A184}  \url{Links.lww.com/CONT/A177}
Parkinson Disease

↓DA in SNc → ↓ Direct + ↑ Indirect = (-) Thalmus
(STN and GPi activity are elevated)

Basal Ganglia
- Striatum: Caudate + Putamen
- Lenticular nucleus: Putman + Globus pallidus
- Subthalamic nucleus
- Substantia nigra
Common Nonmotor Symptoms of Parkinson Disease

• Affective Disorders - depression, anhedonia, anxiety, impulsiveness, hallucinations
• Cognitive Dysfunction - bradyphrenia, memory impairment; anosmia
• Visual Disturbances - impaired color discrimination, visuospatial abnormalities
• Autonomic Dysfunction - orthostatic hypotension
• Gastrointestinal Dysfunction - constipation
• Sexual Dysfunction - erectile dysfunction
• Sleep Disturbance - REM sleep disturbance
Parkinsonian syndromes

Parkinson Disease

Secondary Parkinsonisms
- Vascular
- Infectious
- Drug/toxins
- Metabolic
- Tumor/trauma
- Normal Pressure Hydrocephalus

Hereditary Parkinsonisms
- PARK gene/loci
- Spinocerebellar ataxias
- Huntington disease
- Lubag disease
- Wilson disease
- Neuronal brain iron accumulation disorders

Atypical Parkinsonisms
- Progressive supranuclear palsy
- Corticobasal degeneration
- Multiple System atrophy
- Dementia with Lewy bodies

Modified
Parkinsonian Disorders

- **Idiopathic** – Parkinson disease: sporadic or genetic
- **Secondary**
  - Drugs (neuroleptics such as haloperidol)
  - Metabolic: manganese poisoning (soldering), MPTP exposure, hypothyroidism, low B12
  - Stroke involving basal ganglia
  - Infection (influenza encephalitis)
- **Atypical Parkinsonism**
  - RED FLAGS: early dementia, early falls, prominent ocular dysmotility, prominent dysautonomia, prominent ataxia, poor response to L-dopa
  - Multiple System Atrophy
  - Dementia with Lewy bodies
  - Progressive supranuclear palsy
  - Corticobasal degeneration
Multiple System Atrophy

- Onset age > 30
- Two main types
  - MCA – Parkinsonism
  - MSC – Cerebellar
- **Autonomic failure** 65% vs 5% in Parkinson’s
- *Symmetric* onset rigid bradykinesia
- Atypical tremor: High frequency, low amplitude, jerky, stimulus-sensitive, myoclonic (polyminimyoclonus)
- Hypokinetic dysarthria
- Anterocollis with early postural instability
- Poor response to L-Dopa
  - Early orofacial dyskinesias
- Jaw opening dystonia
- Dementia in < 20% of cases
- Video: links.lww.com/CONT/A179
Glial Cytoplasmic Inclusions
- white mater
- basal ganglia
- brainstem
- cerebellum
Progressive Supranuclear Palsy

Tauopathy

• Onset age <63-66>
• Patients live 5 to 8 years
• Early falls
• **Vertical supranuclear palsy**: downgaze more sensitive
• Frontal dementia with pseudobulbar affect
  – “Applause sign”
• Worried/Astonished look
• Progressive dysarthria: spastic/hypernasal
• Axial rigidity, not stooped
  – Turning is pivoted, not block like with Parkinson disease; “Rocket Sign”
• Video: links.lww.com/CONT/A178
PSP

Hummingbird Sign

Tufted Astrocyte
Corticobasilar Degeneration

Tauopathy

- Asymmetric rigidity with dystonia and ideomotor apraxia
  - Alien Limb phenomenon
- Course rest/action tremor
- Myoclonus
- Cortical sensory loss
- Poor response to L-Dopa
- Diagnosis correlates poorly with autopsy
- Can see asymmetric frontoparietal atrophy on MRI
- Brain with frontal dementia
  - 4R hyperphosphorylated tau in neurons/glia

Video: links.lww.com/CONT/A204
Parkinson Disease Dementia

- 1817 James Parkinson wrote that the intellect was “uninjured”
- 30 to 75% of patients with PD
- Death usually 4 years after onset of dementia
- Risk factors: advanced age, severity/duration of PD, male, postural instability, axial symmetrical parkinsonism, akinetic dominant parkinsonism
- Considerable overlap with DLB: executive/recall dysfunction, visual-spatial impairment, fluctuant attention (may be locked w L-dopa dosage), hallucinations.

Diagnostic Criteria for PDD

• Diagnosis of idiopathic Parkinson Disease
  • Bradykinesia PLUS one of the following:
    – Rigidity
    – 4-6 Hz rest tremor
    – Postural instability not caused by vestibular, cerebellar or proprioceptive mechanism
  • Need three of the following: unilateral onset symptoms, rest tremor, progression, asymmetry, good response to L-dopa, clinical course at least 10 years, hyposmia, visual hallucinations

• Dementia Syndrome:
  – Slow onset, slow progression, develops within Parkinson disease. Involves > 1 cognitive domain, impairs life.
• Presence of Major depression makes diagnosis unreliable.

Emre M. Mov Disord 2007; 22(12):1689-1707
The 5 Cognitive Domains

• **Attention** – Patient shows a level of impairment in concentration, which may fluctuate over time.

• **Executive function** – Impairment in complex thought processes like initiating an action, planning, or organization.

• **Visuo-spatial ability** – Difficulty with sense of direction or spatial relationship between objects.

• **Memory** – Noticeable impairment in both the recall of existing memories and in the learning of new material.

• **Language** – Basic language features may largely be intact, although there may be difficulties in finding words and understanding complex sentences.
DEMENTIA WITH LEWY BODIES
Dementia with Lewy Bodies

• Second most common dementia after Alzheimer's Disease in people older than age 65
• Mean age of onset is 75
• Ascending Spread of Lewy Body Pathology
  1. **Brainstem** (anosmia, depression, REM sleep disorders, arousal/attention, autonomic, movement)
  2. **Limbic** (amnesia/psychosis)
  3. **Cortical** (multidomain dementia)
• How does the disease begin?
Lewy Pathology has been found in the ganglia of Meissner’s and Auerbach’s plexuses years before CNS expression.

Hyposmia, depression, REM sleep disorder may proceed motor and cognitive symptoms in PD and DLB by many years.

May enter via the gut and spread by the dorsal motor nucleus of the vagus.
Dementia with Lewy Bodies

• PD, PDD & DLB may be phenotypic expressions of the same pathologic process.
  – DLB pathology is different from PD only in terms of distribution.
  – Lewy Body disease at autopsy does not predict whether patient had DLB or PDD in life.

• Dementia heralds the onset of illness
  – Classically BEFORE parkinsonism motor signs
    • May present up to one year after motor features

The 4 Clinical Feature of DLB

1. Early Dementia
2. Visual Hallucinations
3. Fluctuating Attention and Arousal
4. Motor Parkinsonism
1: Early Dementia

- The central feature of the disorder
- “1 year rule”:
  - if dementia precedes or occurs within 1 year after onset of motor parkinsonism, then patient has DLB.
  - If motor parkinsonism precedes dementia by at least 1 year, patient has PDD.
- After age 55
- Progressive decline, interferes with social/occupational function
- Deficits of attention, executive function, visual-spatial function
  - Difficulty multitasking, following conversations
  - Getting lost when driving; relying more on GPS devices
- Memory impairment may not be prominent early but usually develops with progression
  - Problems primarily with retrieval rather than memory encoding
  - Unlike with Alzheimer Dementia
- **Mini-Mental State Examination cannot detect mild dementia in PD**; likely true also for DLB.
- Can be difficulty to distinguish PD/DLB from Vascular Dementia, especially if dementia is severe
2: Neuropsychiatric Symptoms

- **Visual Misperceptions: Early**
  - Mistake a stick for an animal, furniture for people in dim lighting

- **Visual Hallucinations: COMMON**
  - Lewy body deposition in posterior temporal cortex
  - Recurrent, complex
  - Well formed, animated, include adults or children
  - Usually not persecutory

- **Delusions: Late**
  - Paranoid quality
  - Home intrusion/theft, infidelity
  - *Capgras syndrome*: spouse has been replaced by an imposter
    - Due to loss of memory valence; patient is no longer able to retrieve emotional associations.

- **Depression/Anxiety are common**
3: Fluctuating Attention & Arousal

- Lewy Body Brainstem deposition
- Presents as staring, daytime fatigue
- Must exclude metabolic and medication effects
  - OSA, Thyroid, B12, UTI, anticholinergics, benzodiazepines
- **Dementia Cognitive Fluctuation Scale**
  1. Does the patient’s inability to organize thoughts in a coherent way vary significantly over the course of the day?
  2. Does the patient spend more than 1 hour sleeping during the day time?
  3. Is the patient drowsy/lethargic for more than 1 hour during the day despite normal night sleep?
  4. Is the patient difficult to arouse on a typical day?
- YES to 3 of 4 Qs: 80% sensitive, 76% specific in differentiating DLB, PDD from AD and vascular dementia.

4: Motor Parkinsonism

• Develop *with or after* Cognitive, Neuropsychiatric and Fluctuating Attention/Arousal
• Motor signs are often symmetric, unlike Parkinson’s Disease
• May see bradykinesia and gait disturbance more than rest tremor; variable.
• Have limited response to carbidopa/levodopa despite dopamine dysfunction.
• Can see generalized myoclonus unlike in Parkinson’s Disease.
• Can see other non-motor Parkinson features like REM sleep disorder, loss of smell, constipation very early. May see dysautonomia late due to cardiac sympathetic denervation.
DAT Scan

Normal Scan

Abnormal Scan
DLB Diagnostic Criteria

- **Central feature**
  - Dementia

- **Core features:**
  - Recurrent visual hallucinations
  - Fluctuations in attention/alertness
  - Parkinsonism motor signs

- **Suggestive Features**
  - REM sleep disorder
  - Severe Neuroleptic Sensitivity
  - Low DAT uptake on SPECT PET scan

- **Clinically Probable DLD**
  - Two Core - or -
  - One Core & One Suggestive

- **Clinically Possible**
  - One Core - or -
  - One Suggestive

- **Supportive Features:**
  - Repeated falls
  - Syncope
  - Severe autonomic dysfunction
  - Transient loss of Consciousness
  - Neuroleptic sensitivity
  - Depression
  - Occipital hypometabolism on PET
  - Abnormal MIBG myocardial scintigraphy
  - EEG slowing with temporal sharp waves

- **Diagnosis less likely in the presence of**
  - Stroke
  - Parkinsonism only appears with onset of severe dementia

Diagnostics

- Always check thyroid function, B12, RPR, CBC, CMP, Liver, Renal, PSG.
- Lumbar puncture: may aid AD diagnosis but not Lewy Body. Reduced Aβ$_{42}$ is associated with cognitive decline in PD.
- MRI brain may show relative preservation of the medial temporal lobe volume in DLB compared to AD
  - Does not establish a diagnosis of DLB, PD or PDD.
- DaT scan abnormality: low false negative in PD; unclear what false negative rate is in DLB.
- PET/SPECT shows occipital hypometabolism in DLB & PD/PDD

Irwin, D. *Nat Rev Neurosci* 2013; 14(9):626-36.
A: Dopamine transporter imaging ($^{123}$I-FP-CIT SPECT)

Control | AD | DLB

B: Blood flow imaging ($^{99m}$Tc-HMPAO SPECT)

Control | AD | DLB
Lewy Body Dementia

TREATMENT
REM Sleep Behavior Disorder

• Frequent in PD and DLB
• 40% of cases of “idiopathic cases” subsequently developed parkinsonism.
• Begins years before cognitive and motor features.
• Caused by α-synuclein in the dorsal pons.
• Normal atonia during REM sleep is lost → “acting out dreams” or periodic limb movements in sleep.
• Need Polysomnogram.
• Treatment: melatonin 6mg, clonazepam 0.25 to 1mg q HS. Carbidopa/L-Dopa may be helpful. Also consider trazodone, mirtazapine or seroquel.
• Avoid dopamine agonists
• zolpidem can cause encephalopathy and sedation.

Cognitive Impairment

• Acetylcholinesterase inhibitors: donepezil, rivastigmine
  – Double-blind, placebo-controlled trials show modest but statistically significant positive cognitive/behavior effects on AD.
  – Reduced cholinergic activity in DLB as been shown; small double-blind/placebo controlled trials of donepezil and rivastigmine in DLB showed improvements in neuropsychiatric symptoms. These medications are well tolerated in DLB.
  – Data for rivastigmine seems better than donepezil in PD/PDD.

• NMDA antagonist: memantine
  – Data is mixed in DLB and PDD

Psychiatric Features

- Cholinesterase inhibitors can be helpful.
- ≥ 50% of patients with DLB are sensitive to neuroleptics.
- Neuroleptics can irreversibly worsen parkinsonism, increase risk for neuroleptic malignant syndrome & increase mortality.
- Neuroleptics can impair attention and alertness.
- Avoid haloperidol, thioridazine, fluphenazine and other typical antipsychotics with D₂ receptor antagonism.
- Avoid benzodiazepines, anticholinergic medications including TCAs.
- Seroquel is safe in PD or DLB. Clozapine may worsen motor symptoms in PD and is more difficult to prescribe.
- Olanzapine worsens motor symptoms in PD but not in DLB.
- Pimavanserin (5-HT2A inverse agonist): FDA approved 2016 for Parkinson’s hallucinations/delusions
- Trazodone (5-H2 agonist) 50mg q HS
- Citalopram, escitalopram, venlafaxine for anxiety/depression
  - Low risk for worsening tremor

Other Symptoms

• Motor
  – Carbidopa/L-Dopa: 33% of DLB respond
  – Start low and go slow
  – 25/100 0.5 tabs TID; increase by 0.5 tab TID per week until 2 tabs TID
  – Do not use ER formulation due to iritic absorption
  – Do not use dopamine agonists due to psychiatric side effects

• Dysautonomia: nocturnal hypotension, orthostatic hypotension, sensitivity to heat or cold, sexual dysfunction
  – Compression stockings, abdominal binders, salt tablets
  – midodrine; fludrocortisone

• Incontinence/bladder spasm
  – Avoid oxybutynin
  – Can use tolterodine, solifenacin, darifenacin, trospium
  – mirabegron (beta-3 agonist) may help raise blood pressure

• Constipation
  – High fiber diet, polyethylene glycol, lactulose
Lewy body composite risk score

Please rate the following physical findings being present or absent for the past 6 mo and symptoms as being present or absent for at least 3 times over the past 6 mo.

<table>
<thead>
<tr>
<th>Does the patient…</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have a loss of postural stability (balance) with or without frequent falls?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have a tremor at rest in any of the 4 extremities or head?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have episodes of illogical thinking or incoherent, random thoughts?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have frequent staring spells or periods of blank looks?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have visual hallucinations (see things not really there)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have orthostatic hypotension or other signs of autonomic insufficiency?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A score of ≥ 3 distinguishes Lewy Body Dementia from other Dementias

97% sensitive
86% specific

Copyright 2013 The Lewy Body Composite Risk Score James E. Galvin, MD, MPH.

## Most Common Lewy Body Dementia Symptoms

<table>
<thead>
<tr>
<th>Dementia</th>
<th>Hallucinations</th>
<th>Cognitive Fluctuations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movement Disorders</td>
<td>Poor Regulation of Bodily Functions</td>
<td>Sleep Problems</td>
</tr>
<tr>
<td>Depression</td>
<td>Anxiety</td>
<td>Apathy</td>
</tr>
<tr>
<td>Agitation</td>
<td>Paranoia</td>
<td>Delusions</td>
</tr>
</tbody>
</table>
Do Not Forget Caregiver Support

- Depression
- Financial Strain
- Disturbed Sleep
- Physical/emotional abuse

Who does the caregiver call in an emergency? Is there access to a geriatric inpatient unit?
Selected References

• Houser M. *npj Parkinsons Disease* 2017. 3: 3
• Lee DR et al *Am J Geriatr Psychiatry* 2014;22(9): 926-935.
• Tiraboschi, P. *Arch Gen Psychiatry* 2002. 59(10): 949-51.