Lewy Body Dementia: Challenges and Treatment

- Karen Mullins, D.O.
- Knoxville Neurology Clinic

Lecture Objectives/ Goals

- Be familiar with signs and symptoms of the pt with LBD
- Review pathophysiology of LBD
- Understand the challenges of treatment
- Review nonpharmacologic treatments of LBD
- Become familiar with pharmacologic therapies currently available to pts with LBD

I have nothing to disclosure
Clinicopathologic Spectrum of Dementia

Clinical Presentation Of LBD

- Fluctuations in cognitive function
- Varying levels of alertness and attention
- Excessive daytime drowsiness or daytime sleep >2 hours
- Episodes of staring off into space
- Episodes of disorganized speech

Clinicopathologic Spectrum of Dementia

Clinical Presentation Of LBD

- Visual hallucinations
- Delusions
- REM sleep behavior disorder
- Impaired executive function, visuospatial function (Stroop, digit span backwards)
Clinical Presentation of LBD

- Parkinsonism
  - Appears early in course of disease
  - May not be enough to meet full criteria for PD
  - Less frequent rest tremor
  - May see myoclonus
  - Orthostatic hypotension

Clinical Presentation of LBD

- Capgras syndrome: delusion that people in the environment are not themselves but actually doubles
- Also see passive personality traits—decreased emotional responsivity, lack of interest in hobbies, increasing apathy, purposeless hyperactivity

Diagnostic Criteria

Dementia with Lewy Bodies (DLB)

- Consensus diagnostic criteria for DLB were first established in 1996
  - Dementia accompanied by ≥ 1 of three core symptoms
    - Fluctuating cognition, visual hallucinations, and motor parkinsonism
- Criteria were expanded in 2005
  - Neuroleptic sensitivity and RBD
  - Specific imaging findings on dopamine SPECT imaging or MIBG cardiac scintigraphy
  - Dementia with progressive cognitive deficits that result in social and occupational dysfunction must be present for either probable or possible DLB

Pathophysiology LBD

- Lewy Bodies- eosinophilic inclusion bodies
- Present in brainstem and cerebral cortex
- See changes in basal ganglia>>reduction in # of cholinergic projections to thalamic reticular nucleus>> reduction in cholinergic neurotransmission
- Specific to LBD: correlation between hallucinations, staring spells and decreased cholinergic function

LBD Pathophysiology

- Primary constituent of Lewy Body is alpha synuclein which is a presynaptic protein
- Neurofilament proteins and ubiquitin are also found
- Numerous neurotransmitters, not just acetylcholine, are decreased in pts with DLB.
- Decrease in Ach may be more severe in DLB pts than in pts with Alzheimer disease.

Are PD and LBD prion disorders?

- Alpha synuclein misfolds in brains of patients with neurodegenerative conditions
- Is the Lewy Body a protective mechanism?
  - Does it clear and segregate misfolded protein aggregates?

Pathophysiology LBD

- Nagahama et al found SPECT scan studies of 145 DLB patients revealed:
  - Visual hallucinations - hypoperfusion of parietal-occipital association cortices
  - Misidentifications - hypoperfusion of the limbic-paralimbic structures
  - Delusions - hypoperfusion of the frontal cortices

Defining Characteristics

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<tr>
<th>Clinical presentation and Symptoms</th>
<th>PDB</th>
<th>LBD</th>
<th>Other Cognitive</th>
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<tbody>
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<td>Hypothalamic, limbic, and autonomic dysfunction</td>
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<td>Motor dysfunction</td>
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<td>Pyramidal signs</td>
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Challenges in LBD

- Disease symptoms fluctuate
- Harder to control
- More sensitive to medications - neuroleptic hypersensitivity
- As dementia occurs earlier in illness, pts often require assistive care earlier
- There are no currently FDA approved medications specifically for treatment of DLB
Treatment Options LBD

- Acetylcholinesterase Inhibitors
- Atypical neuroleptics
- Antidepressants
- Dopaminergic agents
  - Agonists
  - Carbidopa/levodopa

AcetylCholinesterase Inhibitors

- Should be first line treatment
- Donepezil- dose range 5mg initially then 10mg, ?23mg
- Rivastigmine-dosing: oral max 12mg daily
  - Patch 4.6mg- 9.5mg/24 hours
- Galantamine- max 24mg/day

What about Memantine?

- 2010 study of pts with LBD showed improvements on certain cognitive tests
- Well tolerated
- Dosing: 5mg titrating up to 10mg twice daily
Antidepressants

- Serotonin reuptake inhibitors are drug of choice
  - Venlafaxine
  - Paroxetine
  - Fluoxetine
  - Sertraline

Antipsychotics

- Initiate when clinically indicated
  - If pt loses ability to recognize hallucination is not real or hallucinations are frequent
- Use second generation antipsychotics
  - Quetiapine
  - Clozapine
  - Aripiprazole
  - AVOID standard antipsychotics (i.e. Haldol)
  - Cardiac precautions

Carbidopa/levodopa

- First introduced in 1960s
- Still gold standard for Parkinsons disease
- Prefer immediate release to controlled release
- Use smallest dose that controls symptoms
- What should I do about hallucinations?
Parcopa

- Oral disintegrating tablet of carbidopa/levodopa
- Useful in patients who can't swallow or can't get going in the morning
- Useful as "rescue" med

Dopamine Agonists

- Nonergotamine agonists
  - Ropinirole (Requip)
  - Pramipexole (Mirapex)
  - Rotigotine (Neupro)

Dopamine Agonists

- Pramipexole
  - Available in oral form: extended and immediate release
  - Dose: maximum 1.5 mg, three times daily
  - Side effects include: nausea, sedation, leg swelling
Dopamine Agonists

- Ropinirole
  - Oral form, immediate release and extended release
  - Dose range: max 24mg/day
  - Side effects similar to pramipexole

Dopamine agonists

- Rotigotine (Neupro patch)
  - Available in patch form (transdermal)
  - Provides continuous stimulation
  - 3 dosages – 2, 4, 6 mg/24hr

What about rasagiline?

- Selective MAOB inhibitor
- Dosing: can start at 0.5mg once daily or 1 mg daily
- Precautions with certain meds
  - Antidepressants
  - Serotonin syndrome
REM sleep behavior disorder
- Clonazepam 0.5mg-1mg prior to bedtime
- Melatonin- dose varies
- Valerian Root 530mg 2-3 capsules prior to bedtime
- Treat disorder only if occurring on a frequent basis

Nonpharmacologic Options LBD
- No approved surgery (DBS)
- Keep daily routine
- Speak to pt in simple terms
- Door alarms/chimes
- Geropsychiatric evaluation/home health

Nonprescription Options
- Gingko baloba- no benefit, can cause bleeding
- Antioxidants
  - Coenzyme Q10
  - Ubiquinol
  - Ibedenone
  - Vitamin E
- What about B12?
Nonpharmacologic Treatment LBD

- Exercise-PLIE study
- Music therapy
- Yoga/tai chi
- Cognitive exercises
- Adequate nutrition
- Pet therapy

Case Presentation

- 52yo male presents at urging of his wife with complaints of occasional rest tremor and bradykinesia. Pt denies memory “problems” but wife notes pt stares off into space and at times seems agitated. He is having no frank hallucinations but has had a single episode of believing his neighbors are “watching him”.
- The above symptoms started 6 months ago.
Case Presentation Cont’d

- MRI brain is normal.
- EEG reveals mild diffuse slowing.
- CMP, B12, TSH are all normal.
- Exam reveals mild hypomimia, mild intermittent rest tremor with cogwheeling. Pt’s MMSE is 26/30.

Case Presentation Cont’d

- What medication(s) are indicated at this time?
- Would you start an antipsychotic at this point?
  - If so, which one?

You receive a call from pt’s wife 6 weeks later that pt has become agitated and is acting out his dreams on a nightly basis. What treatment is indicated now?

At this pt’s 4 month followup pt’s wife states he is having daily delusions about neighbors stealing from him. Pt has called police twice. He is seeing strangers in his home on a daily basis. What is your next step?

Caregiver Support

- Local support groups
- Websites:
  - wemove.org
  - pda.org
  - lbda.org
  - clinicaltrials.gov
- Home physical therapy, nursing etc.
- Strong social support group
References


Take Home Points

LBD patients should be on an acetylcholinesterase inhibitor early on- SO TREAT EARLY
Use only second generation antipsychotics when indicated
Further research is needed to identify biomarkers allowing earlier diagnosis
Caregiver support is essential