Parkinson’s Disease Dementia

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Question #1

• Have you previously worked with patients who have Parkinson disease with dementia?
  1. Yes, in the last year.
  2. Yes, more than a year ago.
  3. Never.
  4. Unsure.
Objectives

1. Define Parkinson's disease dementia
2. Review characteristics of Parkinson's disease dementia
3. Differentiate Parkinson's disease dementia from other causes of dementia
4. Review management of Parkinson's disease dementia
Case Presentation

- 76 year old man with change in handwriting (micrographia) and walking 14 years ago.
- Diagnosed with Parkinson's disease and responded to levodopa.
- Within first few years he noted mild difficulty with word-finding while speaking.
- **Motor symptoms progressed** very slowly over time and levodopa was increased.
76 year old man

- Worsening cognition and dependence on aides to point of needing 24 hour care.
- Hallucinations at night; worse with quetiapine, currently on aripiprazole
- Freezing of gait
- Anxiety and depressed mood
- Insomnia
Allergies:
None

Medications
- Carbidopa/levodopa 25/100 #2 three times daily
- Aripiprazole 5mg daily
- Clonazepam 0.5mg prn
- Levothyroxine
- Meclizine prn
- Tylenol PM acetaminophen/diphenhydramine prn

76 year old man
Physical Exam:
- Not oriented to place or date.
- Could not perform serial 7’s.
- Significant delay in verbal responses.
- Bilateral bradykinesia and rigidity.
- Mild dystonic dyskinesias of limbs and trunk.
- Shuffling gait and reduced arm swing with freezing of gait on initiation and turns.

MRI brain:
Interval increase in global cortical atrophy. Chronic right lacunar infarct.

76 year old man

Bradykinesia = slowness of movement
Dystonic = sustained involuntary postures
Dyskinesia = involuntary muscle movements associated with PD treatment
Affects >1% of those older than age 60.

**Movement disorder**
- Bradykinesia
- Rigidity
- Rest tremor
- Postural Instability

**Non-motor symptoms**
- Neuropsychiatric
- Disorders of sleep and wakefulness
- Autonomic symptoms

**PARKINSON’S DISEASE**
Cognition in PD

• MCI is present in 15-20% PD patients at diagnosis (Aarsland, 2009).

• Cognitive decline is insidious.

• Typical profile:
  • Impaired attention
  • Deficits in memory (recall not encoding)
  • Impaired visuospatial function
  • Impaired executive function.

• There is heterogeneity in cognitive profile.
PDD Epidemiology

3-4% of dementia patients (Aarsland, 2005)

PERCENTAGE OF PD PATIENTS WHO DEVELOP DEMENTIA ANNUALLY (Emre, 2007)

1/3 of all PD patients in clinic-based studies (Aarsland, 2005)

LIFETIME PREVALENCE (Hely, 2008; Aarsland, 2003).

~10 years

PD

ONSET OF DEMENTIA

(Aarsland, 2003; Hughes, 2000)
PDD Epidemiology

• No studies evaluating racial/ethnic differences in PDD specifically

• In PD, one study found that African-Americans had reduced incidence of PD compared to whites. Incidence of PD in Hispanics was not significantly different. (Dahodwala, 2009)

• For Medicare beneficiaries with PD, frequency of dementia was 78.2% in Blacks, 73.1% in Hispanics, 69% in Whites, and 66.8% in Asians. (Willis, 2012)
PDD Diagnostic Criteria

Core Features

Diagnosis of PD (UK Brain Bank Criteria)

Dementia syndrome with insidious onset and slow progression, developing in the context of established PD, diagnosed by:

- Impairment in more than one cognitive domain
- Representing a decline from premorbid level
- Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment attributable to motor or autonomic symptoms.

(Emre, et al. 2007)
## PDD Diagnostic Criteria

<table>
<thead>
<tr>
<th>Associated Clinical Features</th>
<th>Features that make diagnosis uncertain</th>
<th>Features suggesting other conditions or diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cognitive features</td>
<td>• Co-existence of abnormality which may by itself cause cognitive impairment, e.g. vascular disease</td>
<td>• Acute confusion due to systemic disease or drugs</td>
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<tr>
<td>• Behavioral/neuro-psychiatric symptoms</td>
<td>• Time between motor and cognitive symptoms unknown</td>
<td>• Major depression</td>
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<td>• Probable vascular dementia</td>
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(Emre, et al. 2007)
Probable PDD

Core features:
Both must be present
No features that suggest other diagnosis

Associated clinical features:
No features that make diagnosis uncertain

Typical cognitive profile (2/4 core cognitive domains)
- Impaired executive function
- Impaired visuospatial function
- Impaired attention which may fluctuate

- Presence of at least one behavioral symptom
  - Apathy
  - Depressed or anxious mood
  - Hallucinations / Delusions
  - Depressed or anxious mood
  - Anxiety

- Impaired free recall which usually improves with cueing
- Excessive daytime sleepiness

Probable PDD (Emre, et al. 2007)
Possible PDD

Core features: Both must be present

One or more features that make diagnosis uncertain

No features that suggest other diagnosis

Associated clinical features

- Atypical cognitive profile in one or more cognitive domains, e.g.
  - prominent fluent aphasia,
  - pure encoding-failure amnesia (no improvement with cueing) with preserved attention.
- Behavioral symptoms may or may not be present

(Emre, et al. 2007)
PDD Cognitive Profile

**LANGUAGE:**
- Less impairment than AD

**ATTENTION:**
- Impaired and may fluctuate

**VISUOSPATIAL FUNCTION:**
- Significant impairment, more than AD

**MEMORY:**
- Visual and verbal memory impaired but less than AD. Retrieval more impaired than encoding.

**EXECUTIVE FUNCTION:**
- Impaired, typically more than AD

(Emre, et al. 2007)
PDD Cognitive profile

• Cognitive profile can be used for diagnosis but does not conclusively differentiate diagnoses.

(Emre, et al. 2007)
PDD Neuropsychiatric Symptoms

Psychotic symptoms

Hallucinations
45-65%
Visual > Auditory
More common in PDD/DLB than AD

Delusions
25-30%
Paranoid, “phantom boarder,” misidentification
PDD Neuropsychiatric Symptoms

Mood disorder

- Depression: 40-60%
- Anxiety: 30-50%
- Apathy: 25-50%
PDD Sleep Disorders

• More REM sleep behavior disorder than AD
  • May precede onset of dementia in PD (Postuma 2009)
• Increased daytime sleepiness
• Insomnia
PDD Motor Symptoms

• Advanced motor symptoms.
• Greater axial rigidity and postural instability.
• Increased falls.
Question #2

- Of patients with **PD and dementia** which of the following would meet criteria for **probable PDD**? Choose 1 or more.
  1. Significantly impaired language and attention, hallucinations
  2. Significantly impaired attention and visuospatial function, depression
  3. Significantly impaired attention and memory deficit (encoding), apathy
  4. Significantly impaired executive function and attention, anxiety
Differential Diagnosis

- Dementia with Lewy bodies (DLB)
  - 1-year rule
  - 3rd report of DLB consortium:

  “DLB should be diagnosed when dementia occurs before or concurrently with Parkinsonism, and PD-D should be used to describe dementia that occurs in the context of well-established PD. In research studies in which distinction is made between DLB and PD-D, the 1-year rule between the onset of dementia and Parkinsonism for DLB should be used.”
Differential Diagnosis

• AD with late Parkinsonism
• Parkinsonism and dementia of other disorders
  • Frontotemporal Dementia
  • Vascular parkinsonism/dementia
  • NPH
Risk factors for dementia in PD

• Greater age
• More severe Parkinsonism
  • rigidity, postural instability, and gait disturbance
• Mild cognitive impairment at baseline.
• Inconsistent results:
  • Greater age at onset
  • Male gender
  • Education
  • Depression
  • Visual hallucinations
  • Other clinical features.
PDD **Genetics**

- Genetic associations with increased risk of dementia in Parkinson's disease.
  - *APOE* ε4 allele (Huang, 2006; Morley 2012)
  - *MAPT* H1/H1 (Williams-Gray, 2009)
  - Heterozygous *GBA* mutations (Seto-Salvia, 2012)
  - *SNCA* mutations

- Dementia is less common in PD patients with *PRKN* mutations.
Pathology of PD dementia

• Lewy body pathology in cortex and limbic structures.
  • Hallucinations are indicator of Lewy body pathology (Williams, 2008)

• AD pathology frequently present

• Cerebrovascular pathology
76 year old man

- Assessment
  - Advanced Parkinson's disease with dementia (PDD)
  - Major issues of dementia, insomnia, anxiety, and freezing of gait
Question #3

What about this patient’s history is inconsistent with dementia with Lewy bodies?

1. Visual hallucinations
2. Presence of depressive symptoms and anxiety
3. Parkinsonism preceding dementia by >1 year
Treatments – Dementia

- Cholinesterase inhibitors
  - Donepezil (Aricept)
  - Galantamine (Razadyne)
  - Rivastigmine (Exelon)
- NMDA-receptor antagonist
  - Memantine (Namenda)

Movement Disorders Task Force (Seppi, 2011) concluded rivastigmine is clinically useful and evidence for donepezil, galantamine, and memantine was insufficient.
Treatments – Dementia

• 2012 Cochrane Review concluded that evidence supports use of cholinesterase inhibitors for Parkinson's disease dementia (Rolinski, 2012)
  • Rivastigmine is the only cholinesterase inhibitor with FDA indication for PDD.

• Evidence from clinical trials do not support the use of memantine (Namenda).
Treatments – Dementia

- **Donepezil**
  - 5mg (½-10mg) tablet daily in AM for one week
  - Then 10mg tablet daily in AM
  - If GI side effects, then...

- **Exelon patch**
  - 4.6mg patch q24 hours for 1 month
  - Then 9.5mg patch q24 hours

- While higher doses of each approved, little increased benefit with greater side effects.

- These medications may improve psychosis and other behavioral symptoms.
Treatment - Psychosis

- Reduction in dopaminergic medications
- Elimination of other possible contributory medications – anticholinergics, benzodiazepines
- Rule out metabolic causes of delirium
Treatment - Psychosis

• Atypical antipsychotics with least likelihood of worsening Parkinsonism.
  • Clozapine
    • Only treatment recommended for treatment of psychosis in PD. (Seppi, 2011)
    • Inconvenience of regular blood monitoring for agranulocytosis limits usage.
  • Quetiapine
    • Both have FDA black box warning for increased risk of sudden cardiac death. (Ray, 2009)
• Avoid all other antipsychotic medications.
Treatment - Psychosis

- Reduction in dopaminergic medications, transition toward levodopa-only regimen
- Assess for other causative medications
- Assess causes of delirium
  - Labs, head CT, infection
- Add cholinesterase inhibitor if dementia present.
- Quetiapine 12.5mg, increase as needed unless limited by sedation.
- Clozapine 12.5mg increase as needed.
- Pimavanserin? – Serotonin inverse agonist
Treatment

- Depression
  - SSRI/SNRIs
- REM sleep behavior disorder
  - Environmental modification
  - Benzodiazepines
Movement disorder

• Levodopa primary treatment
  • More effective for bradykinesia and rigidity.
    • Not for apraxia
  • Less side effects

• Medications to avoid
  • Anticholinergic drugs – trihexyphenidyl
  • Amantadine
  • Dopamine agonists
  • MAO inhibitors
76 year old man

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76 year old man
Question #4

What is the best first intervention to address freezing of gait in this patient?

A. Increase each levodopa dose.
B. Add additional levodopa dose and reduce time between doses.
C. Stop aripiprazole
D. Add pramipexole, a dopamine agonist, to reduce ‘off’ periods
Question #5

• What is the best intervention for treatment of dementia in PDD?
  A. There is no good evidence to support any pharmacological intervention.
  B. Add memantine.
  C. Add cholinesterase inhibitor
  D. Both B. and C.
If after stopping aripiprazole and starting a cholinesterase inhibitor, psychotic symptoms continued and were disabling, what would be a reasonable treatment option?

A. Retry quetiapine.
B. Initiate clozapine.
C. Initiate olanzapine.
D. A or B
E. A, B, or C.
76 year old man

Plan

Anxiety
- Anti-depressant
- Consider low-dose benzodiazepines (fall risk)

Dementia
- Cholinesterase inhibitor for dementia and possibly hallucinations to reduce need for antipsychotic.

Insomnia/Anxiety/Depressed mood
- Mirtazapine
- No diphenhydramine (No Tylenol PM)

Parkinsonism/Freezing
- No antipsychotics
- Determine if freezing occurs at end of dose – would consider 4 times a day dosing
References


References


Vision
• A cure for Lewy body dementias and quality support for those still living with the disease.

Mission
• Through outreach, education and research, we support those affected by Lewy body dementias

Family Services
• LBD Caregiver Link (800.539.9767)
• Caregiver support groups
• An active online community

Educational Resources
• Free publications, for families and professionals
• Webinars
• Lewy Body Digest (e-newsletter)
• www.lbda.org

Download free diagnostic and comprehensive symptom checklists from LBDA.org

Order print copies of this 40 page booklet from NIA's Alzheimer's Disease Education & Referral Center
Questions?