Can’t Shake It Off: Neuropsychiatry of Parkinson Disease

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Disclosures

• I have no conflicts of interest
• I will discuss off-label use of medications in this presentation: this is due to limited availability of FDA-approved medications for the conditions under discussion
Objectives

- Describe Parkinson Disease, and identify neuropsychiatric symptoms of PD, including prodromal symptoms
- Describe correlation between neuropsychiatric symptoms and prognosis
- Review treatment approaches to neuropsychiatric symptoms of PD
“A More Melancholy Object I Never Beheld”

- Initial description of “Paralysis Agitans” or Shaking Palsy by James Parkinson in 1817
- Described the motor features of Parkinson Disease (PD) and its progression
- Very limited treatment options
- Many patients died prior to development of neurocognitive symptoms
Presenting Symptoms

- Slowed movements
- Tremor
- Difficulty initiating movements
- Decreased facial expression
Typical appearance of Parkinson’s disease

- Stooped posture
- Masked facial expression
- Rigidity
- Forward tilt of trunk
- Flexed elbows & wrists
- Reduced arm swinging
- Slightly flexed hips & knees
- Trembling of extremities
- Shuffling, short-stepped gait
Substantia nigra degeneration in PD and dementia with Lewy bodies. The core pathology of PD affects the DA-producing neurons of the substantia nigra (SN). DA is produced by SN neurons and transported along the axons of these neurons to the striatum. The triad of rigidity, bradykinesia and tremor at rest, correlates with degeneration of the dopaminergic nigrostriatal pathway and DA depletion in the striatum. In advanced PD, loss of these neurons results in depigmentation of the SN (A) and in loss of the DA synthesising enzyme tyrosine-hydroxylase (TH) (B-C). PD is a synucleinopathy. Fibrils made of insoluble polymers of α-synuclein are deposited in the neuronal body, forming round lamellated eosinophilic cytoplasmic inclusions, the Lewy bodies (D). α-synuclein is also deposited in neuronal processes.
Diagnosis

- Clinical examination
- UPDRS
- DATscan: essential tremor vs. Parkinsonism

**Normal DaT density**
Possible nonparkinsonian syndrome

**Abnormal DaT density**
Possible parkinsonian syndrome

DaTscan will be distributed in the striata and appear as mirrored comma or crescent shapes if dopaminergic neurons are intact or not affected\(^1\,\!^5\).

A decrease in DaTscan activity will result in period or oval shapes and reduced image intensity on one or both sides\(^1\,\!^5\).
Neuropathology of PD

• Neurodegenerative process: multiple etiologies
• Affects multiple neurotransmitter systems: Dopamine (DA) primarily
  – But also norepinephrine, acetylcholine, and serotonin
• Brain regions affected
  – Basal ganglia (initial locus of disease): bradykinesia, akinesia, rigidity
  – Locus coeruleus: neuropsychiatric effects
  – Cortex: coordination of movements, neuropsychiatric effects, neurocognitive effects
More Than Shaking!!!!

• Cognitive Impairment
• Depression
• Pseudobulbar affect
• Apathy
• Impulse control disorders
• Psychosis
• Sleep and wakefulness
Cognition in PD

• Cognitive deficits (less common in tremor predominant)
  – Mild Cognitive Impairment
    • Subcortical dysfunction
    • Executive dysfunction
    • Retrieval memory impairment
  – Dementia in 30-40% of cases
    • More significant memory impairment
    • Language, visuospatial impairments
    • Variable executive dysfunction (DA dysfunction)
Cognition in PD

• New(ish) criteria for diagnosis for PDD from MDS (2007)
  – Multi-domain cognitive impairment
  – Decline from premorbid level
  – Deficits impair daily function
  – Associated features
    • Impaired attention, impaired executive function, impaired visuospatial function, impaired memory, language
    • Apathy, personality changes, hallucinations, delusions, excessive daytime sleepiness
Cognition in PD

• Cognitive deficits can be identified even early in disease course
  – Some patients more amnestic, others more dysexecutive
  – No clear association between pattern of deficit and progression of disease

• Memory concerns less frequent presenting symptoms than in AD (67% vs. 100%)
Parkinson Disease Dementia

• Risk factors:
  – Older age and higher severity of EPS
  – Less tremor-predominant
  – Suboptimal response to L-dopa
  – Dystonic dyskinesias
  – REM sleep behavior disorders

• Development of dementia leads to more severe motor course
  – Risk factor for falls, orthostasis
Imaging in PDD

- Intermediate pattern of atrophy in MRI between AD, PDD, and normal controls
  - No consistent pattern differentiating between illnesses on structural imaging

- Multiple areas of hypoperfusion on SPECT/PET in PDD
  - Multiple locations in association cortex
  - Similar topographical patterns between PDD and Dementia with Lewy Bodies (DLB)
  - Decreases in glucose metabolism in occipital visual cortex, inferior parietal cortex in PDD
Genetic Aspects of PDD

• Correlation with ApoE2, E4 alleles
  – Some positive studies, other negative ones

• Dementia described in familial forms of PD including PARK1 and PARK8

• Some studies suggest familial aggregation of PDD
Treatment of PDD

- Family and patient psychoeducation
- Occupational therapy, speech therapy
- Medication treatment
  - Rivastigmine approved for PDD
  - Potential side effects
  - May reduce risk of falls as well as psychiatric symptoms of PD
  - Memantine effective in one study, ineffective in another study
    - Risk of hallucinations
Neuropsychiatric Symptoms of PD

• Depression
  – Full-criteria MDD less common; most frequently seen in akinetic/rigid cases
• Anxiety (often comorbid with depression)
• Apathy
• Psychosis
  – VH, delusions (non-complex)
• Nightmares, REM sleep behavior disorder, nocturnal verbalizations, myoclonus
• “On/off” phenomena, obsessions, punding, hypersexuality, paraphilias
• impulse control disorders, dopamine dysregulation syndrome
Depression in PD

- Depression shown to have significant negative impact on quality of life
  - Higher frequency of hopelessness, suicidality, social withdrawal
  - MDD patients experience greater cognitive decline, deterioration in ADLs, and faster advance through stages of PD
- Greater impact on QOL than motor symptoms of PD
- Treatment leads to improvement in ADLs over time
Diagnostic Challenges

• Focus on motor symptoms in treatment
• Patient/family self-report
• Screening measures include somatic symptoms
  – Overlap between MDD and PD
• Differentiating apathy from depression
• Range of types
  – MDD, minor depression, adjustment disorders
• Lack of recognition of risk of depression as an illness
  – “Of course you’re depressed!”
  – Stigma, pts fear discussing it until symptoms are profound
Depression Treatment

• Psychoeducation

• Psychotherapy
  – Supportive, grief therapy, insight-oriented, CBT
  – Family/caregiver therapies

• Rehab services including PT, OT, speech

• Appropriate social supports, in-home care, meaningful activities, socialization

• Medication treatments

• ECT
Antidepressant Treatments

- SSRIs
- Tricyclic Antidepressants
  - Attention to side effects
- Dopamine agonists
- Rivastigmine
- Amantadine
Parkinson Disease Psychosis

- Originally seen as primarily due to dopamine stimulation to mesocorticolimbic D2/D3 receptors
  - However, dose and duration do not clearly correlate with psychosis in many cases
  - May relate to hypersensitivity of receptors in dopamine-depleted state
  - Cholinergic deficiencies and dopamine-serotonin imbalances also implicated
  - Neurodegeneration of limbic, paralimbic, neocortical gray matter including PFC also associated with PDP
Parkinson Disease Psychosis

• Symptoms frequently include:
  – Visual hallucinations most commonly; complex, formed hallucinations
    • People, family members, animals, machines
  – Auditory, tactile, olfactory also seen
  – Delusions less common
    • Paranoia, “phantom boarder”
    • Typically less complex than seen in primary psychotic disorders
**Parkinson Disease Psychosis**

- Presence of at least one:
  - Illusions
  - False sense of presence
  - Hallucinations
  - Delusions

- Differs from DSM-V criteria
  - Includes wide range from mild to severely ill

- Studies demonstrate higher rates of dementia, more severe PD symptoms, and more neuropsychiatric and sleep disturbance symptoms in pts with PD-psychosis
  - Cognitive impairment may predict later psychosis
Parkinson Disease Psychosis

- Patients with longer duration of disease at higher risk for psychotic symptoms
  - Progression of disease from mild perceptual abnormalities to frank psychosis and dementia
  - Parallels progressive motor, cognitive symptoms and neuronal loss
- More helpful to consider a spectrum of psychotic symptoms rather than binary presence/absence
- Treatment recommendations can then be more responsive to stage of disease
  - Ex: psychoeducation and reduction of anti-PD medications in early stages rather than antipsychotic treatment
Psychosis in PD

- Treatment of cognitive deficits may also decrease psychotic symptoms
  - Use of acetylcholinesterase inhibitors inversely related to psychotic symptoms in some studies
- Subtypes of PD may allow improve prognostication and potential more aggressive symptom management
  - Postural instability-gait disturbance (PIGD) subtype along with hallucinations lends higher risk of dementia
  - Neuropathologic demonstration of higher burden of cortical Lewy bodies as well as cortical amyloid-beta plaque deposition
Parkinson Disease Psychosis

- Pimavanserin approved for psychosis in PD dementia
  - Concerns with its use
  - No medicines approved for non-dementia related PD psychosis
- Antipsychotic medications bring safety complications
  - Concern with increased fatality in first year of use
- Quetiapine commonly used clinically
  - Lower affinity for DA receptor
  - No support from controlled clinical trials for this strategy
- Two RCTs supporting positive effect of clozapine in PDP
  - Monitoring/safety issues with this medication
Additional Non-Movement Symptoms

• Apathy in up to 40% of patients
• Non-motor fluctuations in affect, “on-off” states
• Pseudobulbar affect
• Disorders in sleep and wakefulness
  – 90% of pts have some type of sleep/wakefulness problem
  – Include RLS, REM sleep behavior disorder, hypersomnia, insomnia
• Impulse control disorders
  – Gambling, shopping, sexual behavior, eating problems relatively common
  – Underreported and frequently under-recognized
Additional Non-Motor Symptoms

- Dopamine Dysregulation Syndrome
- Punding (unclear frequency)
The present and the future…

• “Non-motor” symptoms of PD result in significant disability, worse quality of life, poorer clinical outcomes, and increased caregiver burden

• Recent advances
  – Expert consensus diagnostic criteria for PDD, PDP
    • Impacts clinical management and high-quality research
  – Improvements in reliability and availability of screening tools
  – Further appreciation for neural effects of PD and associating localization of pathology with cognitive and psychiatric functioning
The present and the future…

• However:
  – Low recognition of these symptoms
  – Treatments remain limited
  – Core treatments for PD can both help and hurt these symptoms
  – Limited core research into the occurrence, disease course, risk factors, and optimal management strategies for these illnesses
The present and the future…

• Improving recognition and treatment of neuropsychiatric symptoms of Parkinson Disease will allow people with PD to live longer and with better quality of life.
Selected References


• Kalia, Lorraine V et al. Parkinson’s Disease. The Lancet, Volume 386, 9996:896 - 912


Selected References


Thank you!