Parkinson’s Disease: Motor and Nonmotor Features
OhioHealth Neuroscience Symposium
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Outline

• Epidemiology of Parkinson’s Disease
• Motor features
• Nonmotor features
• Medical Treatments
• Surgical Treatments
• Nonpharmacological Treatments
  • Therapy
  • Exercise
• Local Resources/Support
Dr. James Parkinson 1817 “Paralysis Agitans” - London surgeon with apothecary practice
Later renamed “Parkinson’s Disease” by Charcot
Parkinson’s Disease: Epidemiology

• The second most common neurodegenerative disease
  – 1-3% of adults over age 65
  – Incidence increases rapidly over 60 years of age with mean age at diagnosis 70.5 years old
Cardinal (Motor) Features of PD

1) Bradykinesia
2) Rigidity
3) Resting tremor

Postural instability
Mood disorder
Apathy, depression, anxiety

Excessive sweating
(diaforesis)

Flexed posture

Reduced arm swing

Micrographia

Gait disturbance
Start hesitation, short shuffling steps

Cognitive changes
Mental slowing/dementia

Sleep disturbance
Insomnia, nightmares, sleep walking

Reduced facial expression
Reduced blinking, Parkinsonian ‘stare’

Drooling (sialorrhoea)

Quiet, monotonous speech

Lead-pipe rigidity
+/- cogwheeling

Rest tremor

Urinary retention, frequency, impotence

Postural instability/falls
Parkinson’s Disease

One of the most important guiding principals: **individualize care**

Examples:
- Young onset PD with limb dystonia
- Early tremor dominant PD
- Longstanding PD with motor fluctuations and memory decline
- Postural instability gait disturbance (PIGD) variant

No definitive medication is neuroprotective
  – oxidative stress, neuro-inflammation, autophagy, anti-alpha synuclein therapy
Cut section of the midbrain where a portion of the substantia nigra is visible.

Substantia nigra

Diminished substantia nigra as seen in Parkinson's disease.
Treatment of Motor Symptoms

- Rigidity, bradykinesia, and rest tremor
  - Gold standard: carbidopa/levodopa
    - Especially when difficulty with ADLs
  - Dopamine agonists (pramipexole, ropinirole, rotigotine transdermal)
    - Consider in younger patients (<age 50)
    - Caution in patients with cognitive/renal issues
    - Impulse control disorders (ICDs), extremity swelling, sleep attacks
  - MAO B inhibitors (rasagiline and selegiline)
    - Potential reaction with serotonergics/sympathomimetics
      - Randomized control trials: safety with sertraline 100 mg/day, fluvoxamine 150 mg/day, trazodone 100 mg/day, and amitriptyline 50 mg/day
    - No true definitive neuroprotective benefit – ADAGIO
  - Amantadine –dyskinesia, tremor reduction or freezing of gait
  - Surgery: Deep brain stimulation therapy, Duopa, others
Treatment of Motor Symptoms

- Focal dystonia: Trihexiphenidyl (caution anticholinergic effects) or botulinum toxin injections
- End of Dose Wearing off (EDWO)
  - COMT inhibitors (Entacapone), dopamine agonists, MAO B inhibitors, levodopa
    - Overall decrease in “off” time from 1-2 hours a day
  - Carbidopa/Levodopa extended release
  - Deep brain stimulation therapy (DBS)
  - Carbidopa/Levodopa intestinal gel infusion (Duopa)
    - If poor DBS candidate due to age or cognitive/behavioral issues
  - Ultrasound
- Levodopa Induced Dyskinesia (LID)
  - Peak dose – Amantadine
  - Diphasic – Dopamine Agonists
  - DBS
  - Duopa

A word about dyskinesia: many patients will not be aware of dyskinesia until moderate in degree or will not mention as wearing off is more clinically bothersome to them until dyskinesia impacts gait
**Surgical options**

- **DBS**
  - Blocks electrical signals from target (STN in most PD, Gpi in ET)
  - Tip of electrode in area to be stimulated
  - Extension (insulated wire) under the skin
  - Neurostimulator in chest wall
    - Settings altered initially frequently - then every few months
    - Patient may adjust on own within thresholds
  - PD with motor fluctuations
    - “Best on” effect of levodopa
    - May reduce medication by 50%
    - Patient selection important
    - Concerns: cognitive impairment, high fall rate, significant depression → suicide risk

- **MR-guided focused ultrasound pallidotomy**
  - Pilot study 2015: PD with dyskinesia
  - Not DBS candidate/patient choosing not to undergo DBS
Surgical options

Carbidopa/Levodopa intestinal gel
• Carbidopa/levodopa 5 mg/mL/20 mg/mL in a stable methylcellulose gel through gastrostomy tube with jejunal extension
• Pump/dopamine cassette carried with patient in belt region
• Infusion with capability of bolus dosing
• Labor intensive for patients/caregivers
• Hardware issues: Infection, occlusion, or displacement
Parkinson’s Disease Therapy

Physical Therapy

Goal-directed motor skill learning:
1) Repetition
2) Intensity
3) Challenge and skill training

Prefrontal cognitive circuits involved in early phases of motor learning
• Cognitive engagement used:
  • Feedback (verbal or proprioceptive)
  • Cueing (visual, auditory, and/or tactile)
  • Dual tasking

• Lee Silverman LSVT BIG therapy
  • Defined protocol
Parkinson’s Disease Therapy

**Occupational Therapy**
- Fine motor skills impairment
- Difficulty with ADLs
- Tremor (especially combined PD/Essential Tremor patients)

**Speech Therapy**
- Hypophonia
  - Improve speech volume (emphasis on pitch and volume)
  - When enunciation and reading aloud has failed
- AAN practice parameter 2006
  - Lee Silverman Voice Technique (LSVT): maximize phonation and effort
    - Time intensive
- Dysphagia
  - Small bites, chin tuck, double swallow, avoid problem foods; diet modification, applesauce/pudding with pills. Consider Barium swallow.
Parkinson’s Disease Exercise

- Evidence supporting best type and long term benefits are limited
- If safe for the patient should be a part of the regimen
- Some early studies with potential improvement in quality of life
  - Yoga
  - Ballroom Dance (tango)
  - Tai chi (6 week program twice weekly)
  - Cycling (forced)
  - Silver Sneakers
  - Group exercise therapy
    - OhioHealth Delay the Disease – pilot trial data
  - Boxing
    - Rock Steady (Grandview)
  - Music therapy
    - Dempsey Family Library at RMH
  - Others
    - Gerlach Center for Senior Health
  - Cognitive exercises: crossword puzzles, Sudoku, card games, read newspaper, Scrabble, Lumosity/other
    - Encourage low cost
OhioHealth Delay The Disease

www.delaythedisease.com
David Zid, BA
Jackie Russell, RN, BSN

• Group and one-on-one exercise classes (some free, some fee based)

• Training for healthcare professionals

• Books and DVDs

• Care partner seminars
Nonmotor Features

• High frequency of occurrence
• Can occur before motor symptoms
• Impact health related quality of life
  – Can be more bothersome to patients than motor features
  – Important in prognosis
• Physicians often simply do not ask
Nonmotor Features

Mood disorders
- Depression
- Anxiety
- Psychosis
- Impulse Control Disorders (ICDs)

Cognitive disturbance
- Mild Cognitive Impairment
- Subcortical dementia
- Other forms of dementia

Autonomic features
- Orthostatic hypotension
- Bowel/bladder issues
- Constipation
- Sexual dysfunction
- Seborrhea
- Sialorrhoea

Sleep disturbance
- REM behavioral disturbance
- RLS/PLMS
- Obstructive Sleep Apnea

Other
- Fatigue, anorexia, sensory disturbance, weight loss
Nonmotor etiology

- Lewy-type alpha-synucleinopathy (LTS) outside the nigrostriatal pathway
  - Clinical and autopsy studies
  - In multiple organs including heart, GI tract, submandibular gland, skin, spinal cord
    - Example: Hyposmia
      - olfactory bulb, primary olfactory cortex
Nonmotor Features of PD Phenotypes

- Brainstem route
  - Consequent phenotype
    - Brainstem dominant (often with late onset hyposmia)
- Olfactory to limbic
  - Limbic dominant (often with anosmia)
- Cognitive (Neocortical subtype)
  - Cognitive dominant (late onset PD)
- NMS dominant profile (subtype)
  - Sleep dysfunction (RBD/EDS)
  - Dysautonomia (Adrenergic)
  - Depression/Anxiety
  - Fatigue (Sertonic?)
  - Central Pain (Opioidergic?)
  - Weight loss
  - Amnestic MCI (Cholinergic)
  - Apathy
  - Anxiety
  - Falls with cognitive impairment

Movement Disorders
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Mood Disturbances in PD

• Depression
  – Related to PD or may precede the disease itself
    • Up to 5 years before motor onset
  – Insufficient dopaminergic drive
  – Can be improved with dopaminergic medications
    • Evidence of improvement with dopamine agonists and MAO-B inhibitors
  – Clinically significant in 40-50%
  – Beck Depression Inventory (BDI) as screening tool
  – Neuropsychological testing
  – Meds: No clear consensus
    • Nortriptyline, citalopram, paroxetine, venlafaxine efficacious. Paroxetine CR was not.
    • Extrapyramidal SE can occasionally occur with SSRIs (sertraline least likely)
    • SSRIs with MAO B inhibitors - potential risk of serotonin syndrome
    • Tricyclics: faster response but more cognitive SE
  – Exercise may stimulate endogenous dopamine
    • Pilot trial: early participation in a group exercise program has significant effect on symptoms of depression
      – mean improvement in Beck Depression Inventory 1.07 points
Mood Disturbances in PD

• Anxiety
  – Related to PD or precede the disease itself
    • May precede by up to 20 years
  – 31% point prevalence meta-analysis: 49 articles related to PD and anxiety
    • Generalized Anxiety Disorder (GAD) 14%, Obsessive-compulsive disorder (OCD), social phobia 13.3%, and anxiety NOS 13.3%, panic disorder 6.8%
  – LRRK2 gene mutation carriers (G2019S) anxiety higher in carriers than in noncarriers
  – Panic, phobia, and social phobia also more common
  – Locus coeruleus and raphe nuclei
  – Evidence of improvement with dopamine agonists and MAO-B inhibitors
  – Insufficient evidence for carbidopa/levodopa
  – Usually SSRI with anxiolytic properties
Mood Disturbances in PD

- **Apathy**
  - Lack of motivation, decreased interest and emotion
  - Common and can be disabling in PD
  - Prevalence 15-70%
  - Improves with levodopa and DA in PD patients
  - Possible cholinergic denervation
    - Benefit on rivastigmine when pure apathy without depression or anxiety
  - In advanced PD often associated with dementia
  - Difficult to treat

- **Impulse Control Disorders (ICDs)**
  - Excessive gambling, binge eating, excessive shopping, and/or hypersexual behavior
  - Often underreported
  - Dopamine agonists (ropinirole, pramipexole, rotigotine transdermal)
    - Risk factors: younger age, male gender, previous addictive behavior
    - Dose-dependent

- **Neuropsychiatric nonmotor fluctuations**
  - ON euphoric and OFF dysphoric states \(\rightarrow\) Dopamine dysregulation syndrome/dopamine addiction
Mood Disturbances in PD

- **Psychosis**
  - Medication-related
    - Reduce or discontinue systematically in reduced order of potency
  - Acute medical illness (infection, delirium)
    - UA, CNS imaging, labs
    - Avoid anticholinergics > age 70 or patients at risk
  - Structural CNS lesion – evaluate with MRI/CT
  - Parkinson’s Disease Psychosis
    - Hallucinations in up to 40% of advanced PD patients
      - Risk factor for nursing home placement and mortality
    - In a 12 year PD study of 230 PD patients with psychosis: 60% developed hallucinations or delusions
      - Risk factors: higher levodopa dose, RBD history, dementia, low ADL function (UPDRS-II)
    - Medications
      - Atypical antipsychotics favored in low dosages
        - Quetiapine 12.5-100 mg qhs treatment of first choice
      - Pimavanserin (selective serotonin 5-HT2A receptor inverse agonist)
      - Typical antipsychotics and some atypicals (including risperidone and olanzapine) can cause drug induced parkinsonism
Cognitive disturbance

• MCI
  – Greater than age–related changes
  – No difficulty with ADLs
  – 95% PD MCI are across multiple domains rather than single domain
    • working memory, visuospatial, language, executive
  – Increases the risk for PD Dementia
  – “Rule of thirds”
  – Evaluate for mood, medication, or sleep issues contributing to memory
Cognitive disturbance

- **Dementia**
  - Recall, cognitive, and social issues impairing ADLs
  - Parkinson’s Disease Dementia (PDD)
    - Subcortical
    - Executive dysfunction
    - Other: vascular, Alzheimer’s, mixed, mindful of atypical parkinsonism (Lewy body disease etc)
  - Dementia = one of strongest clinical predictors of long term care placement
  - Consider Hospice
Cognitive Disturbance Treatment

- **Meds:**
  - Donepezil or rivastigmine should be considered for dementia in PD (Level B)
- Cognitive social worker
- Living situation
- Driving status - DRIVE assessment
- Financial issues
- Social engagement
- Caregiver support
- Improved quality of life: Gerlach Center, activities/exercise/community engagement
- Movement for memory DTD class
Autonomic Dysfunction

- **Sialorrhea**
  - Reduced oromotor control
  - Mild symptoms:
    - chewing gum/hard candy, increase hydration
  - Moderate drooling:
    - Glycopyrrolate 1 mg tid (anticholinergic side effects)
    - Sublingual atropine (1% ophthalmic solution, 1-2 drops sublingually once daily or BID)
  - Botulinum toxin injections should be considered (Level B)
    - 32 patients with 50 U Botulinum toxin type A in each parotid gland
    - Clinical practice: 500 U botulinum toxin type B in each parotid gland
    - Decreased drooling frequency and familial and social disability
    - No adverse effects in trial; potential for worsening dysphagia exists
Autonomic Dysfunction

• Orthostatic hypotension (OH)
  – Symptomatic drop of 20 mm Hg in systolic or 10 mm Hg drop in diastolic blood pressure
    • Midodrine
      – FDA approved
    • L-threo-dihydroxyphenylserine (L-threo DOPS = Droxidopa)
      – FDA approved
    • Indomethacin, fludrocortisone, pyridostigmine or domperidone with insufficient evidence in PD
Autonomic Dysfunction

• **Erectile Dysfunction (ED)**
  – Rule out treatable causes first
  – Sildenafil citrate 50 mg possibly efficacious
    • May be considered (Level C)
Autonomic Dysfunction

• Constipation
  • Polyethylene glycol may be considered (Level C) to improve bowel movement frequency and stool consistency
  • Insufficient data with botulinum toxin injections
Sleep

- **Excessive Daytime sleepiness (EDS)**
  - Modafinil (Level A) should be considered to improve patient perception of wakefulness but without objective improvement
  - Consider sleep referral especially if snoring

- **Insomnia and sleep fragmentation**
  - **Melatonin**
    - Produced by pineal gland
    - Regulates circadian rhythm
    - Small benefit 5-50 mg
    - Determined effective in improving patient perception of sleep
  - **Carbidopa/levodopa extended release**
    - Improves nighttime akinesia scale
    - Insufficient in improving patient perception or objective measures
  - In patients who have undergone Deep Brain stimulation (DBS) STN therapy, possible improved sleep quality in advanced PD
Sleep

• Fatigue
  – Rule out other medical causes
    • B12, folate, TSH, basic labs
    • Methylphenidate may be considered (Level C) but potential for abuse exists
    • 10 mg PO tid vs placebo for 6 weeks trial
    • Primary outcome measures: Fatigue severity score and Multidimensional Fatigue Inventory
Sleep

• Restless Legs Syndrome (RLS)
  – 20% patients
  – Ropinirole or pramipexole
    • FDA approved for RLS but insufficient evidence in PD with RLS
  – Carbidopa/Levodopa ER
    • Decreases frequency of spontaneous nighttime leg movements

• Periodic Leg Movements of Sleep (PLMS)
  – Carbidopa/Levodopa should be considered (Level B)
  – Insufficient evidence for DAs
Sleep

- REM behavioral disorder (RBD)
  - Parasomnia with acting out vivid/violent dreams
    - Difficult for bed partners
    - Clonazepam or melatonin
      - Insufficient evidence in PD with RBD but useful in RBD
  - Known risk factor for PD Psychosis
Summary

- The cardinal motor features of Parkinson’s Disease include rigidity, bradykinesia, and resting tremor.
- Nonmotor features are often under recognized in PD but highly influence health-related quality of life.
- The most common nonmotor features in PD are: Mood disorders, Cognitive disturbance, Autonomic features, and Sleep disturbance.
- Lewy-type alpha-synucleinopathy (LTS) outside the nigrostriatal pathway may explain PD nonmotor features.
- Medications and PT/OT/ST/exercise may provide benefit and enhance quality of life.
- Surgical options can useful in select patients with PD with medically refractory tremor or disabling motor fluctuations.
- Consider senior centers and local resources/support groups to keep patients active and engaged.
- Consider OhioHealth movement disorder neurology referral!
Local Resources/Support

- Delay The Disease
- Gerlach Center
  - Amy Weeks, cognitive social worker
  - Yoga
  - Classes
  - Activities
- Dempsey Family Library
- NPF Ohio
References

• Adler CH and Beach TB. Neuropathological Basis of Nonmotor Manifestations of Parkinson’s Disease. Mov Disord 2016;31(8):1114-1119.


References


References