Non-motor Symptoms:
What’s New?

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Journal Editing
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Medical Consulting
– Acadia
– Adamas
Tremor
Rigidity
Bradykinesia

Abnormalities of sensation
Sleep disorders
Autonomic dysfunction
Fatigue
Behavioral Changes
Braak Staging of PD

Braak Staging of PD

Early Nonmotor Features

- Impaired olfaction
- Constipation
- Erectile dysfunction
- REM sleep behavior disorder
- Depression
- Anxiety
### Onset of Constipation in Relation to Motor Symptoms

<table>
<thead>
<tr>
<th>Onset of Constipation</th>
<th>Total # (%)</th>
<th>Men # (%)</th>
<th>Women # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before PD</td>
<td>49 (50.5)</td>
<td>23 (43.4)</td>
<td>26 (59.1)</td>
</tr>
<tr>
<td>After PD</td>
<td>14 (14.4)</td>
<td>11 (20.8)</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>34 (35.1)</td>
<td>19 (35.8)</td>
<td>15 (34.1)</td>
</tr>
<tr>
<td>Total</td>
<td>97 (100.0)</td>
<td>53 (100.0)</td>
<td>44 (100.0)</td>
</tr>
</tbody>
</table>

In patients who had onset of constipation before onset of PD, the mean age at which constipation began was 39.9 years.

In these individuals, constipation began a mean of 18.7 years before the appearance of motor symptoms.

Impact of Nonmotor Features of PD

May develop early in the course of PD
- May precede the development of motor features

May become dominant features in advanced PD
- May impair quality of life more than motor features

Major cause of hospitalization in PD
Major cause of institutionalization in PD
Abnormalities of Sensation

Olfactory Impairment

Pain

Visual Dysfunction
Olfactory Dysfunction

Impaired sense of smell
  • Elevated threshold
  • Impaired odor identification

Some impairment in 70-90%

Impairment is selective
  • Licorice, coconut and banana especially impaired
  • Chocolate, strawberry, onion, and others not affected

May develop very early
  • May precede other features
Visual Dysfunction

Symptoms may include:

• “Tired eyes”
• Blurred vision
• Intermittent double vision
  » Reported in 14% of PD patients
• Difficulty reading
• Difficulty seeing in dim lighting
Visual Dysfunction

Routine eye exam often normal

Findings may include:

- Convergence insufficiency
- Impaired color perception
- Abnormalities of blinking
- Reduced contrast sensitivity
Inner Retinal Layer Thinning

Possible mechanisms:

- Retinal dopamine neuron loss
- Dysfunction in other parts of the “visual brain

Treatment of Visual Dysfunction

Impaired contrast sensitivity
  video game playing???
Intermittent diplopia
  prisms
Convergence insufficiency
  eye-focusing exercises
    - “pencil push-ups” and others
Blepharospasm or apraxia of eyelid opening
  botulinum toxin injections
Pain

- An often neglected component of PD
- Exact prevalence is unclear
- Occurs in a variety of forms
- Has been divided into 5 types
Pain

Musculoskeletal
Neuropathic/Radicular
Dystonic
Central
Akathisia
Treatment of Pain in PD

- Adjust PD meds if pain occurs as an “off” phenomenon
- Muscle relaxant medications are not usually effective
- PT or surgery if the pain is due to a pinched nerve
- Botulinum toxin injections if the pain is due to dystonia
- Central pain is resistant to treatment
Autonomic Dysfunction
Autonomic Symptom Survey

Cardiovascular
Gastrointestinal
Urological
Sexual
Thermoregulatory

Cardiovascular Dysfunction
Cardiovascular Dysfunction

- Cardiac sympathetic denervation
- Orthostatic hypotension
- Postprandial hypotension
123I-MIBG Myocardial Scintigraphy

Orthostatic Hypotension

Drop in blood pressure with standing

Occurs in 58% of persons with PD

- Produces symptoms in 20%
- Without symptoms in 38%

Medications may magnify
Orthostatic Hypotension

Lightheadedness is the typical sensation

- May progress to fainting

Other symptoms may also occur

- Disturbances of vision
- Impaired thinking
- Headache in a “coat hanger” distribution
- Lower back or buttock ache
- Lethargy or fatigue
Goals of Treatment

- Decrease symptom frequency & severity
- Restore function (standing and walking)
- Prevent fainting and falling
- Minimize BP increases when laying down
Treatment of Orthostatic Hypotension

**Non-pharmacologic treatment**

**Immediate**
- drinking 12-16 oz. of ice water
- physical maneuvers

**Chronic**
- increase fluid and
- increase salt consumption
- elevate head of bed
- abdominal binder
- pressure stockings

**Pharmacologic treatment**
- fludrocortisone
- midodrine
- pyridostigmine
- droxidopa
- Others (less supportive evidence)
  - Octreotide
  - Yohimbine
  - Desmopressin
  - Caffeine
  - Domperidone
Treatment of Orthostatic Hypotension

Symptomatic nOH occurs when s-SBP falls below the range of cerebrovascular autoregulation

Orthostatic stressors

Medications*

Reduced blood volume

Cerebrovascular autoregulation

Symptoms
**Postprandial Hypotension**

- Blood pressure drops after meals
- Sitting or standing may accentuate
- Carbohydrates are most likely to trigger
- May develop within 15 minutes of eating
- May persist up to 3 hours

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“Nondipping” in PD

Gastrointestinal Dysfunction
Gastrointestinal Symptoms

Excess Saliva in PD

- Experienced by 56-78%
- Initially nocturnal drooling
- May progress to “handkerchief” stage
- Saliva production is actually decreased
- Drooling is due to:
  - Decreased swallowing frequency
  - Decreased swallowing efficiency
  - Tendency for mouth to be open
  - Stooped posture

Treatment of Salivary Excess

- Hard Candy Use
- Sublingual Atropine or Glycopyrrolate
- Intraparotid Botulinum Toxin
- Tympanic Neurectomy
Dry Mouth in PD

- Saliva production actually is reduced in PD
- Causes dry mouth in some individuals
- Medications can accentuate the dryness
- May increase the risk of cavity formation
- May increase the risk of periodontal disease
Treatment of Dry Mouth

Artificial saliva products (Biotene)
  - contains xylitol and glycerin
Pilocarpine (Salagen)
Cevimelene (Evoxac)
Halitosis in PD

More common in persons with PD

Multiple factors contribute

- Dry mouth
- Inadequate brushing/cleaning
- Gum (periodontal) disease
- Bacteria in the mouth
- Inadequate fluid intake

Treatment involves

- Adequate cleaning of teeth and mouth
- Alleviating dry mouth
Gastroparesis

Gastroparesis Symptoms

- Reduced appetite
- Early satiety (fullness after a few bites)
- Nausea
- Vomiting (sometimes undigested food)
- “Heartburn” (gastroesophageal reflux)
- Abdominal bloating and distension
- Weight loss

Treatment - Prokinetic Agents

Dopamine antagonists
- Domperidone - Not available in the USA; rising concern for cardiotoxicity
- Metoclopramide (Reglan) - Do NOT use in PD – crosses the BBB

Motilin agonists
- Erythromycin - Effective acutely when given iv; not ideal for long term use

Histamine H2 antagonist/cholinomimetics
- Nizatidine (Axid) - Only one small pilot study

Ghrelin agonists
- Relamorelin (RM-131) - Still experimental; positive reports in diabetic GP

Serotonin 5-HT4 agonists (increase ACh release)
- Cisapride and tegaserod withdrawn
- Mosapride, prucalopride, and renzapride not available
- RQ-10 - currently experimental; clinical trial underway

Pfeiffer RF. Gastrointestinal and Swallowing Disturbances in Parkinson’s Disease.
Treatment: Possible Approaches

Botulinum toxin injections of the pyloric sphincter

Gastric pacemaker implantation


Circumventing Gastroparesis

Bypassing the stomach

- Levodopa/carbidopa intestinal gel
- Subcutaneous apomorphine
- Rotigotine
Small Intestinal Bacterial Overgrowth in PD

- Not well-studied in PD
- Present in 54% of PD patients in one study
- Is characterized by:
  • Increased bacterial density in the small intestine
  • Presence of colonic-type bacterial species in the small intestine
- Results in malabsorption
  • Might explain weight loss in PD
- Impaired GI motility favors its occurrence

### Small Intestinal Bacterial Overgrowth in PD

Prevalence of gastrointestinal symptoms in patients with Parkinson's disease affected by SIBO versus those without SIBO

<table>
<thead>
<tr>
<th>Symptom</th>
<th>SIBO positive, % (n = 26)</th>
<th>SIBO negative, % (n = 22)</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal discomfort</td>
<td>30.8</td>
<td>27.3</td>
<td>ns</td>
</tr>
<tr>
<td>Bloating</td>
<td>69.2</td>
<td>31.8</td>
<td>2.07 (1.42–16.40)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>65.4</td>
<td>36.4</td>
<td>1.74 (1.01–10.83)</td>
</tr>
<tr>
<td>Constipation</td>
<td>73.1</td>
<td>81.8</td>
<td>ns</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19.2</td>
<td>9.1</td>
<td>ns</td>
</tr>
</tbody>
</table>

Small Intestinal Bacterial Overgrowth in PD

Levodopa Dose Failure

- Competition with protein for intestinal absorption
- Dysphagia with vallecular sequestration of levodopa tablet
- Hiatal hernia with impaired gastric emptying
- Gastroparesis
- Helicobacter pylori infection
- Small intestinal bacterial overgrowth

What Causes Constipation in PD?

- Colon transit time is prolonged in PD
- Slowing occurs in 80% of PD patients
- Average CTT in PD is twice as long: 44 hours vs. 20 hours (Edwards et al.)
- Other investigators report much longer times
Treatment of Colonic Dysmotility

- Increase Dietary Fiber
- Increase Dietary Fluid
- Fiber Supplements
- Stool Softeners
  - Polyethylene Glycol Electrolyte Solution (Miralax)
  - Chloride Channel Activator (lubiprostone)
  - Enemas
- Osmotic Laxatives (lactulose, sorbitol)
- Guanylate cyclase agonist (linaclotide)
Defecatory Dysfunction

- Develops in 66% of PD patients
- Characterized by:
  • Increased straining
  • Painful defecation
  • Incomplete emptying
Normal Defecation

Relaxation of:
- Internal anal sphincter
- External anal sphincter
- Puborectalis

Contraction of:
- Abdominal wall muscles
- Diaphragm
- Glottic muscles

Treatment of Defecatory Dysfunction

- Dopaminergic medications
  – Apomorphine injections
  – Conventional DA agonists
  – Levodopa
- Botulinum toxin
  – External anal sphincter
  – Puborectalis
- Biofeedback techniques

Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson’s Disease.
Pfeiffer RF. Intestinal Dysfunction in Parkinson’s Disease.
In: Parkinson’s Disease and Nonmotor dysfunction, 2nd Edition (Pfeiffer RF, Bodis-Wollner I, Eds), 2013, pp. 155-171
Urinary Dysfunction
Irritative Urinary Symptoms

The most common urinary problem in PD
- Occurs in 53-83% of affected persons
Consists of overactive bladder contraction
Characteristics include:
- Frequent urination
- Night-time urination
- Urination of small amounts
- Urinary urgency
- “Urge” type incontinence
Irritative Symptoms: Treatment

Anticholinergic drugs (older)
  – Are nonselective muscarinic blockers
  – Cross the blood-brain barrier
    • Oxybutynin
    • Tolterodine

Anticholinergic drugs (newer)
  – More selective (M3 receptor)
  – Do not cross the blood-brain barrier
    • Trospium
    • Darifenacin
    • Solifenacin

Beta-3 adrenergic agonist drugs
  – Mirabegron
Irritative Symptoms: Treatment

Botulinum toxin injections
Detrusor muscle

Sacral nerve stimulator

Kulaksizoglu H, Parman Y. Parkinsonism Relat Disord 2010;16:531-534

Wallace PA, Lane FL, Noblett KL. Am J Obstet Gynecol 2007;197:96.e1-5
Obstructive Urinary Symptoms

Less common urinary problem in PD

Causes 23-36% of urinary symptoms

Characteristics include:

- Hesitancy
- Weak urinary stream

May develop overflow incontinence
Obstructive Symptoms: Treatment

Alpha-1 adrenergic antagonists
- Terazosin
- Doxazosin
- Tamsulosin

5-Alpha-reductase inhibitors
- Dutasteride
- Finasteride

Parasympathomimetic agent
- Bethanecol

Intermittent catheterization
Sexual Dysfunction
Sexual Dysfunction in PD

Reduced or impaired function

– In men
  • Erectile dysfunction (39-79%)
  • Decreased desire (44-84%)
  • Decreased orgasm (87%)

– In women
  • Reduced vaginal sensitivity (??%)
  • Decreased desire (71-83%%)
Erectile dysfunction
– PDE5-inhibitors
  • sildenafil, tadalafil, vardenafil
– Sublingual apomorphine
– Intrapenile injections of vasoactive drugs
  • alprostadil, papaverine

Decreased libido
– Testosterone

Inadequate lubrication
– Lubricants
Thermoregulatory Dysfunction
Thermoregulatory Dysfunction

Has not received wide attention in PD
Probably more common than recognized
Two primary manifestations:

• Hyperhidrosis
• Hyperthermia/Hypothermia
Hyperhidrosis in PD

Present in over 50% of persons with PD
Primarily involves the head and neck
Consists of sudden, drenching sweats
Typically occurs in two situations:
  • As a “wearing-off” phenomenon
  • During episodes of dyskinesia
But may occur in persons on no medication
Treatment of Hyperhidrosis

- Adjustment of dopaminergic therapy
  • To reduce “off” time
  • To reduce dyskinesia
- Subthalamic DBS
- Botulinum toxin injections*
  
  *If sweating is localized to armpits
Fatigue
Fatigue

In a recent study was the most frequent nonmotor symptom in persons with PD

- Present in 58%

In another study:

- Ranked as the worst PD symptom by 33%
- Named as one of their 3 most disabling symptoms by 58%
Treatment of Fatigue in PD

Modalities reported to be beneficial:
- Exercise
- Methylphenidate
- Modafinil
- Memantine
- Caffeine
- PD medications
  - Amantadine
  - Rasagiline
  - Pramipexole
  - Levodopa
- Behavioral interactions
Respiratory Dysfunction
Respiratory Dysfunction

Lower airway obstruction
Upper airway obstruction
Restrictive pulmonary abnormalities
Treatment of Respiratory Dysfunction in PD

• Adjust PD medications to reduce “off” time
• Adjust PD medications to reduce dyskinesia
• Treat anxiety if present
• Treat obstructive sleep apnea if present
• Inspiratory and expiratory muscle strength training
Summary

Nonmotor features

- are varied and multiple in PD
- may be present early in the course of PD
- may precede the development of motor features in PD
- may be the source of greater disability than motor features, especially in advanced PD
- impair quality of life throughout the course of PD
- may prompt hospitalization or institutionalization

Effective treatment often exists
QUESTIONS?

Yes, teacher, me has question...

Why you so boring?
Allied Team Training for Parkinson's Disease (ATTP®)

MARCH 27-30, 2019
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Resources

**National Helpline**
Available at 1-800-4PD-INFO or Helpline@Parkinson.org
Mon- Friday 9 am to 8 pm ET

**Podcast: Substantial Matters**
New episodes every other Tuesday featuring Parkinson’s experts highlighting treatments, techniques and research.
Parkinson.org/Podcast

**Fact Sheets and Publications**
Get the resources and information you need to start living a better life with Parkinson’s.

**Aware in Care Kit**
Includes tools and information for people with PD to share with hospital staff during a planned or emergency hospital stay.
Parkinson.org/Awareincare