Gastrointestinal Dysfunction in Parkinson’s Disease

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“…so much are the actions of the muscles of the tongue, pharynx, &c. impeded by impaired action and perpetual agitation, that the food is with difficulty retained in the mouth until masticated; and then as difficultly swallowed”

“the saliva fails of being directed to the back part of the fauces, and hence is continually draining from the mouth”

“the bowels, which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power: the expulsion of faeces from the rectum sometimes requiring mechanical aid”

Gastrointestinal Symptoms in PD

# Gastrointestinal Symptoms in PD

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>Control</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total no. (%) of NMS</strong></td>
<td>8.4 (4.3)</td>
<td>2.8 (2.6)</td>
<td>&lt;0.001 b</td>
</tr>
<tr>
<td><strong>Gastrointestinal tract, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sialorrhea</td>
<td>89 (56.0)</td>
<td>6 (6.1)</td>
<td>&lt;0.001 b</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>32 (20.1)</td>
<td>3 (3.0)</td>
<td>&lt;0.001 b</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (9.4)</td>
<td>4 (4.0)</td>
<td>0.142</td>
</tr>
<tr>
<td>Constipation</td>
<td>67 (42.1)</td>
<td>7 (7.1)</td>
<td>&lt;0.001 b</td>
</tr>
<tr>
<td>Bowel incontinence</td>
<td>9 (5.7)</td>
<td>5 (5.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Incomplete bowel emptying</td>
<td>51 (32.1)</td>
<td>12 (12.1)</td>
<td>&lt;0.001 b</td>
</tr>
</tbody>
</table>
Gastrointestinal Dysfunction

- Excess saliva
- Dysphagia
- Nausea/Gastroparesis
- Bowel dysfunction
  - Decreased frequency
  - Defecatory dysfunction
- Weight loss
Salivary Excess
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 Excess Saliva

• Gum and hard candy
  – Make swallowing more “conscious” and more frequent

• Anticholinergic drugs
  – Avoid systemic drugs such as trihexyphenidyl or benztropine
  – Glycopyrrolate avoids central (brain-related) adverse effects but not peripheral ones
  – Sublingual atropine ophthalmic solution
  – Oral tropicamide films also being tested

Treatment of Excess Saliva

- **Intraparotid botulinum toxin injections**
  - Benefits last for 3-4 months
  - Risk of pharyngeal muscle weakness

- **Antiparkinson medication**
  - May improve swallowing efficiency

- **Behavioral swallowing therapy**

Dysphagia
Dysphagia in PD

- Survey studies report dysphagia in 30-82%
  - Broad range probably reflects questionnaire detail
- Objective testing abnormalities range higher
  - MBS shows some abnormality in 75-97%
  - Patients may be clinically asymptomatic
- Aspiration present in 15-56% of patients
- Clinically silent aspiration present in 15-33%

Dysphagia in PD

- Abnormalities at multiple levels
  - Oral - lips, tongue, mouth
  - Pharyngeal - throat
  - Esophageal - esophagus
- Oropharyngeal phase involves:
  - 30 pairs of striated muscles
- Impaired motor control due to:
  - Rigidity
  - Bradykinesia
  - Tremor (lingual)
- Decreased pharyngeal sensation due to pharyngeal sensory nerve involvement may also play a role

Dysphagia in PD: Other Causes

- Zenker’s diverticulum
- Cricopharyngeal bar
- Achalasia
- Anterior osteophytes
Treatment of Dysphagia

Modified Barium Swallow Test

Abnormal
- Cricopharyngeal Bar
  - Myotomy
  - Swallow Therapy
  - PEG Tube
- Disordered Swallow (PD)
  - Adjust PD Meds
  - Diverticulotmy
  - Swallow Therapy
  - PEG Tube
- Zenker’s Diverticulum
  - Diverticulotmy
  - Swallow Therapy
  - PEG Tube

Normal
- Visualize Esophagus
  - Disordered Motility (PD)
    - Adjust PD Meds
    - Antacids
    - Proton Pump Inhibitors
    - Surgery
  - GERD
    - Adjust PD Meds
    - Antacids
    - Proton Pump Inhibitors
  - Achalasia
Nausea/Gastroparesis
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


Gastric Emptying Results of $^{13}$C-OBT

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 22)</th>
<th>PD patients (n = 36)</th>
<th>UPDRS (0–30) (n = 11)</th>
<th>UPDRS (31–60) (n = 19)</th>
<th>UPDRS (61–92) (n = 6)</th>
<th>H&amp;Y (0–2) (n = 21)</th>
<th>H&amp;Y (2.5–5) (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEC</td>
<td>3.00 ± 0.41</td>
<td>2.33 ± 0.67***</td>
<td>2.50 ± 0.49</td>
<td>2.34 ± 0.67</td>
<td>1.99 ± 0.93</td>
<td>2.54 ± 0.57</td>
<td>2.04 ± 0.71*</td>
</tr>
<tr>
<td>$t_{1/2b}$ (min)</td>
<td>107.31 ± 9.9</td>
<td>169.0 ± 42.3***</td>
<td>147.0 ± 24.2</td>
<td>171.00 ± 37.7</td>
<td>203.0 ± 61.5†</td>
<td>149.7 ± 28.2</td>
<td>196.0 ± 44.8**</td>
</tr>
<tr>
<td>$t_{lagb}$ (min)</td>
<td>70.1 ± 10.2</td>
<td>105.1 ± 32.4***</td>
<td>90.7 ± 14.8</td>
<td>106.5 ± 33.8</td>
<td>127.4 ± 41.6‡</td>
<td>93.5 ± 19.3</td>
<td>121.4 ± 39.9**</td>
</tr>
<tr>
<td>$t_{peak}$ (min)</td>
<td>73.6 ± 19.0</td>
<td>111.3 ± 28.8***</td>
<td>100.9 ± 30.1</td>
<td>111.3 ± 28.0</td>
<td>130.0 ± 22.6</td>
<td>102.9 ± 25.2</td>
<td>123.0 ± 30.1*</td>
</tr>
</tbody>
</table>

May be evident in early untreated PD
More prominent as disease advances
May interfere with absorption of levodopa and other agents

Hermanowicz N. Mov Disord 2008;23:152-153

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 appropriate 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 gastroparesis

- Serotonin 5-HT4 agonists (increase ACh release)
  - Cisapride and tegaserod withdrawn
  - Mosapride, prucalopride, and renzapride not available

**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 Intestine

Here Be Dragons

Join a prairie boy as he finds himself in uncharted waters on Vancouver Island and in marriage. As the ancient cartographers said of the unknown, "Here Be Dragons".
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 SI
  - Presence of colonic-type bacterial species in SI
- 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><strong>Bloating</strong></td>
<td><strong>69.2</strong></td>
<td><strong>31.8</strong></td>
<td><strong>2.07 (1.42–16.40)</strong></td>
</tr>
<tr>
<td>Flatulence</td>
<td><strong>65.4</strong></td>
<td><strong>36.4</strong></td>
<td><strong>1.74 (1.01–10.83)</strong></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

Bowel Dysfunction
Bowel Dysfunction in PD

- Constipation (colonic inertia)
  - Decreased bowel movement frequency
- Defecatory dysfunction
  - Difficulty with the act of defecation
Constipation

• Defined as follows:
  – Fewer than 3 bowel movements weekly
• Occurs in 20-79% of PD patients

Pfeiffer RF. Parkinsonism Relat Disord 2011;17:10-15.
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
What Causes Constipation in PD?

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

Pfeiffer RF. Parkinsonism Relat Disord 2011;17:10-15.
Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson’s Disease.
Pfeiffer RF. Intestinal Dysfunction in Parkinson’s Disease.
Colon Transit Time in PD

GI Transit Time – And More
Prokinetic Agents

- Serotonin 5-HT-4 agonists
  - Cisapride
  - Tegaserod
  - Prucalopride

- Type 2 chloride channel activators
  - Lubiprostone (Amitiza)

- Guanylate cyclase 2 agonists
  - Linaclotide (Linzess)

- Cholinesterase inhibitors
  - Pyridostigmine (Mestinon)

- Prostaglandin analogs
  - Misoprostol (Cytotec)

- Ghrelin agonists
  - Relamorelin (RM-131)

- Surgical approaches
  - Colectomy

Pfeiffer RF. Parkinsonism Relat Disord 2011;17:10-15.
Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson’s Disease.
Pfeiffer RF. Intestinal Dysfunction in Parkinson’s Disease.
Treatment of Colonic Dysmotility

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

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

Pfeiffer RF. Parkinsonism Relat Disord 2011;17:10-15.
Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson’s Disease.
Pfeiffer RF. Intestinal Dysfunction in Parkinson’s Disease.
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Normal Defecation

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

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

Defecatory Dysfunction: Pathophysiology

- Impaired motor control/coordination:
  - Inadequate sphincter relaxation
  - Failure of anorectal angle to open
  - Insufficient intra-abdominal pressure

- Underlying mechanisms may include:
  - Bradykinesia
  - Rigidity
  - Dystonia (off-period phenomenon)

Pfeiffer RF. Parkinsonism Relat Disord 2011;17:10-15.
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
Anorectal Testing in PD

Anorectal manometry

Fig. 4. Anorectal manometry during squeeze maneuver in a control (top) and Parkinsonian subject (bottom). In the control subject, after a rapid initial rise in pressure, a small decline to a sustained squeeze increment follows. While the PD subject generates a similar initial squeeze, this is followed by a more dramatic decline to a lower sustained squeeze increment. Also note the prominent phasic component present in the PD subject.

Fig. 3. Defecography in a PD subject. Frames from each maneuver in sequence; top left, rest; top right, squeeze; bottom left, strain; and bottom right, evacuate. Note (i) anorectal angle decreases rather than increases on straining, an example of paradoxical puborectalis contraction, and (ii) this subject was unable to evacuate the rectal contents.

Anorectal Testing in PD

Before apomorphine

After apomorphine

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
When, Where and Why Does GI Dysfunction Develop in PD?
### Table 3 Incidence of PD according to frequency of bowel movements

<table>
<thead>
<tr>
<th>Bowel movements/d</th>
<th>Sample size</th>
<th>Incident PD cases</th>
<th>Incidence, rate/10,000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>289</td>
<td>10</td>
<td>Unadjusted: 19.6</td>
</tr>
<tr>
<td>1</td>
<td>4371</td>
<td>66</td>
<td>Unadjusted: 8.0</td>
</tr>
<tr>
<td>2</td>
<td>1704</td>
<td>17</td>
<td>Unadjusted: 5.2</td>
</tr>
<tr>
<td>&gt;2</td>
<td>426</td>
<td>3</td>
<td>Unadjusted: 3.8</td>
</tr>
<tr>
<td>Test for trend</td>
<td>—</td>
<td>—</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>Overall</td>
<td>6790</td>
<td>96</td>
<td>7.5</td>
</tr>
</tbody>
</table>

### 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.

Pathophysiology of GI Dysfunction in PD

• Is it based within the
  – Enteric Nervous System?

• Is it based within the
  – Central Nervous System?
Enteric Nervous System
Braak Staging of PD

Braak H, Del Tredici-Braak K. Neuroanatomy of Parkinson’s disease.
Braak: Gastric Involvement

Enteric Lewy Bodies in PD

- Esophagus
  - 1984 – Qualman et al.

- Colon
  - 1987 - Kupsky et al.
  - 1990 - Wakabayashi et al.
  - 1995 – Singaram et al.

Qualman SJ, et al. Gastroenterology 1984;87:848-856
Dopamine in Whole Mounts of Colon

Control subject

PD patient

Alpha-Synuclein Positive Submucosal Neurites in PD in Humans

Obtained during colonoscopy

Lebouvier et al., Gut 2008;57:1741-1743
α-Synuclein in Colon Submucosa - Early PD

Obtained during sigmoidoscopy

Colonic Biopsy 2-5 Years Before PD Diagnosis

• Low Power

• High Power

**Increased Intestinal Permeability in PD**

- PD subjects exhibit increased large intestinal permeability.
- They also demonstrate increased intestinal mucosal staining for E. coli, nitrotyrosine, and alpha-synuclein.

Intestinal Epithelial Barrier in PD


Paracellular Transit

Transcellular Transit
Dysbiosis in PD

- Gut microbiota (100 trillion organisms) and their metabolic products are in close proximity to the ENS.
- Certain types of bacteria may be reduced in PD (e.g. Prevotellaceae) and others may be increased (e.g. Enterobacteriaceae).
- May produce an altered, pro-inflammatory chemical environment.
- With altered intestinal permeability and increased entry of pathogens.
- All of which may trigger ENS pathology.
- And this prompts speculation about Fecal Microbiota Transplantation as a treatment for PD.

Vagotomy and PD

- The risk of developing PD is reduced in individuals who have undergone full truncal vagotomy.
- The risk of developing PD is not reduced in individuals who have undergone superselective vagotomoy.

“Although unable to trace the connection by which a disordered state of the stomach and bowels may induce a morbid action in a part of the medulla spinalis, yet taught by the instruction of Mr. Abernethy, little hesitation need be employed before we determine on the probability of such occurrence.”

But Wait.........
Central Nervous System
Oral Rotenone and GI Functions

No Loss of Enteric Neurons in PD

**ENS α-Synuclein**

- Phosphorylated α-synuclein deposition
  - Follows a rostral-caudal gradient in the ENS
- Follows the distribution of vagal efferents
  - Lower esophagus and stomach
  - Small intestine and proximal colon
  - Upper esophagus is spared
  - Is supplied from nucleus ambiguus

6-OHDA SN Lesion Produces Gastroparesis

SNpc 6-OHDA Alters Neurochemical Phenotypes in Myenteric Plexus

Decrease in TH-IR+ fibers

Decrease in ChAT+ neurons

Increase in nNOS-IR neurons

Totti L, Travagli A. Am J Physiol Gastrointest Liver Physiol 2014;307;G1013-G1023.
GI Dysfunction in PD

- There is pathology in the ENS in PD
- There is pathology in the CNS in PD
- PD may well have its genesis in the ENS
- But it is not so clear whether the GI symptoms of PD are ENS or CNS in origin
- Or perhaps they are both
QUESTIONS?

Yes, teacher, me has question...

Why you so boring?