The Gut-Brain Connection and Parkinson’s disease

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You are in the right space!
We will start at noon.
Overview of talk

• Gut-brain connection in PD
• GI symptoms in PD
• Management of GI symptoms in PD
• Gut-related concerns in medication management
• Dietary considerations
Glossary

• Alpha-synuclein: protein whose abnormal form misfolds and clumps together contributing to PD

• Microbiome: the collection of non-human cells in the body (mainly bacteria, but also viruses, fungi, parasites)
  – Gut microbiome: microbes found in the gut

• MDS-UPDRS: Movement Disorders Society Unified Parkinson’s Disease Rating Scale
The Gut-Brain Connection
Does PD start in the gut?

Perez-Pardo et al., Eur J of Pharm 2017
Does PD start in the gut?

- Alpha-synuclein deposits can be seen in the gut prior to development of motor symptoms of PD
- Enteric nervous system connects to the brain via the vagus
- Gut microbiome differences between PD and non-PD patients
- Gut bacteria metabolize gut contents
- The products of bacterial metabolism
  - May be involved in inflammation
  - May regulate the conversion of alpha-synuclein into disease-forming deposits
- Changes in the gut microbiome such as small intestinal bacterial overgrowth (SIBO), common in PD → “leaky gut” → systemic and/or neuro-inflammation
- Alpha-synuclein deposits may travel from the gut into the brain via the vagus nerve
PD Microbiome

• Increased
  – Akkermansia
  – Lactobacillus
  – Bifidobacterium

• Reduced
  – Prevotella
  – Faecalibacterium
  – Blautia
  – Lactobacillus

• Leaky Gut?
  • Increased short-chain fatty acid production
  • Inflammation
  • Increased formation of toxic alpha-synuclein types
  • Increased clumping of alpha-synuclein
Does PD start in the gut?

- Mouse model
- WT = wild-type (normal)
- ASO = genetic cause of PD (increased alpha-synuclein)
- SPF = specific pathogen-free (normal microbiome)
- GF = germ-free
- Abx = extremely high dose antibiotics (not recommended for humans!)
- Ex-GF = infused with microbiome from PD patients

Differences noted in motor function, alpha-synuclein inclusions, microglia activation (immune system)

Sampson et al., Cell 2016
Does PD start in the gut?

- Vagotomy = cutting the vagus nerve
- Snca -/- = mice who are missing alpha synuclein genetically
- Vagotomy in humans was associated with lower risk of subsequent PD

Kim et al., Neuron 2019
However...

- PD is associated with slow gut function which can alter gut microbiome
  - Chicken vs egg
- Most microbiome studies enrolled PD patients on medications which might alter the microbiome
- PD may begin in the olfactory bulb and spread to brainstem and subsequently or concurrently to gut
Small Intestinal Bacterial Overgrowth (SIBO)

• Found in 25% of PD patients
  – Compared to 15% of healthy older adults
• Associated with worse motor function
• Diagnosed via breath testing
  – Hydrogen
  – Methane
• Treated with specific antibiotics and temporary dietary restriction
• Do not start anti- or probiotics without guidance from an MD
Implications for PD patients

• Vagotomy?
  – high risk and very likely too late to be effective

• Probiotics?
  – Two trials showed benefit for constipation in PD
  – One RCT showed reduced total MDS-UPDRS (\textit{L. reuteri} and \textit{L. fermentum})
  – Bacteria in most commercial probiotics do not survive in the gut due to stomach acid
  – Theoretical risk of inducing or worsening SIBO
  – Some probiotics contain tdc-producing bacteria

• Prebiotics (undigestible fibers that help healthy bacteria)?
  – Barley
  – Soybeans
  – Raw oats
  – Legumes
  – Onions, garlic, leeks
  – None specifically tested in PD

• Antibiotics?
  – Treatment of small intestinal bacterial overgrowth (SIBO)

• Fecal transplantation?
  – No RCT evidence yet of benefit (small open-label study showed benefit)

Xue et al., 2020
GI Symptoms in PD

- **Constipation**
  - Slow-transit
  - Sphincter dysfunction
- **Delayed stomach emptying**
  - Early satiety
  - Bloating

- **Dysphagia** (trouble swallowing)
- **Drooling** (due to reduced frequency of swallowing)
- **Low appetite**
Evaluation of GI Symptoms in PD

- GI evaluation may include
  - Swallow evaluation
  - Endoscopy/colonoscopy
  - Colon transit time
  - Gastric emptying study

- Consultation with a registered dietician

Benninga et al. 2016
Management of GI Symptoms in PD

- Management of swallowing issues
  - Dysphagia diet depending on testing e.g., Pureed foods/ thickened liquids
  - Small bites and sips
  - Alternate liquids and solids
  - Preventive clear / swallow
  - Eat only upright, chew slowly
  - Avoid high risk foods such as whole nuts, dry crackers, pretzels, tough meats

- Management of constipation:
  - Colace (docusate) 100 mg twice a day.
  - Miralax 17 gram (one capful) in 4-8 oz of liquid daily or every other day
  - Dulcolax as needed
  - Fiber:
    - Soluble can reduce cholesterol and blood glucose and forms a gel; helps w/digestion
    - Insoluble: best for constipation
    - Psyllium = combination of soluble & insoluble fiber, not highly fermented
    - Inulin/Dextrin = fermented insoluble fiber, not useful for constipation
  - Water!
  - Exercise!

- Prescription strength gut motility medications
  - Linzess, Amitiza
Management of GI Symptoms in PD

• Treatment of delayed gastric emptying
  – Blenderized foods
  – Domperidone*
  – Erythromycin
  – NO metoclopramide (exacerbates PD symptoms)

• Treatment of drooling
  – Botulinum toxin (e.g., Xeomin) injection to salivary glands

*Not available in US
Gut bacteria inhibits levodopa action

Side effects: nausea, lightheadedness

Positive effects: reduced tremor, bradykinesia, rigidity
Gut bacteria inhibits levodopa action

Maini Rekdal et al., Science 2019
What affects levodopa metabolism?

• Levels of specific bacteria:
  – Enterococcus faecalis and Eggerthella lenta

• Levels of specific enzymes:
  – tyrosine decarboxylase from E. faecalis

• Specific SNPs (gene variant) from E. lenta gene that codes for a specific enzyme (dopamine decarboxylase, dadh)

  • Maini Rekdal et al., Science 2019
Prolonged use of levodopa and disease duration are associated with increased \textit{tdc} gene-carrying bacteria

- Altered levels of gut dopamine  \implies  Impaired GI motility  \implies  SIBO  \implies  worsening of motor fluctuations  \implies  higher doses  \implies  vicious cycle

- In small intestinal bacterial overgrowth (SIBO) associated with PPI use, \textit{Enterococcus} tends to dominate

- Prolonged use of levodopa appears to favor growth of \textit{tdc} bacteria, further lowering efficacy of levodopa

- May identify biomarker for proper levodopa dose

- Some Probiotics contain \textit{tdc} gene-carrying \textit{Enterococcus}

Van Kessel et al., Nature Communications 2019
Carbidopa does not block bacterial metabolism

- Carbidopa blocks human peripheral decarboxylase enzyme
  - Making levodopa more present in serum and thus brain
  - BUT NOT BACTERIAL decarboxylase!
- Alpha-fluoromethyl-tyrosine (AFMT), an amino acid, can block bacterial tyrosine decarboxylase
  - Making levodopa more avail in mice serum
  - potential rx for managing motor fluctuations
- Maini Rekdal et al., Science 2019
What does this mean for PD patients?

- As GI symptoms progress, the gut can slow down, impacting onset of action of levodopa
- Typically levodopa should be taken on an empty stomach as protein in the gut can interfere with the absorption of levodopa
  - Med should be taken at least 30-60 minutes prior to having a meal
  - If a meal will be skipped the medication should still be taken on time
  - Med can also be taken 60 minutes after finishing a meal
- Constipation should be treated aggressively
Helpful Hints for Medication Consistency

• Taking medications on an empty stomach
• Taking medications at consistent times every day
• Preventing fluctuations of dopamine levels in the brain
  – Reduce risk of developing dyskinesias
  – Reduce risk of ON/OFF fluctuations

• Medication sets
  – Fill once a week
  – Help to verify that pills have or have not been taken but do not remind patients

• Medication alarms
  – Available as a watch or on a smart phone
  – Will not verify that the med has been taken if patient silents an alert without taking the medication.

• MedReady
  – Alerts a family member or caregiver when medications have not been taken within a certain amount of time.
### Dietary Choices in PD

- **MIND diet:** Mediterranean Intervention for Neurodegenerative Delay

<table>
<thead>
<tr>
<th>What's on the MIND Diet?</th>
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<tbody>
<tr>
<td><strong>At least three servings of green salad and one other vegetable each day</strong></td>
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<tr>
<td><strong>At least a one-ounce serving of nuts</strong></td>
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<tr>
<td><strong>Beans or legumes at least every other day</strong></td>
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<td><strong>Poultry at least twice a week</strong></td>
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<td><strong>Fish at least once a week</strong></td>
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<tr>
<td><strong>A five-ounce glass of red wine each day</strong></td>
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<td><strong>No more than one tablespoon a day of butter or margarine; choose olive oil instead</strong></td>
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<tr>
<td><strong>Cheese, fried food and fast food no more than once a week</strong></td>
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<tr>
<td><strong>Pastries and sweets less than five times a week</strong></td>
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- **Other considerations:**
  - Dysphagia
  - Weight Loss
  - SIBO
  - Delayed Gastric Emptying
  - Neurogenic Orthostatic Hypotension
  - Religious or other dietary restrictions

- **Do your best!**
  - Don't let perfect be the enemy of good.