PD And The Gut

Sneha Bharadwaj
4th Aug 2017

NMS in PD

1. Neuropsychiatric disorders
2. Sleep disorders
3. Sensory symptoms
4. Autonomic disorders
   • Gut disorder - most common

Doi et al, Movement Disorders, 2014
GIS In PD

- Determine quality of life
- Associated with severe complications
  - malnutrition, pulmonary aspiration, intestinal obstruction, megacolon, perforation
- Most common cause of ED presentation in PD
- Impact other PD symptoms
- DGE & Gastroparesis
  - delayed intestinal transit
  - erratic absorption of levodopa
  - motor fluctuations

Cloud et al, Curr Neurol Neurosci Rep (2011)

DGE

- Common in early and advanced PD
  - Upper GI symptoms
  - Under detected in routine practice
  - Under reported by patients
  - Likely neurohormonal aspects of brain-gut axis
- Symptom complex
  - nausea, vomiting, heartburn, postprandial epigastric / abdo pain, bloating

Marrinan et al, MDS 2014
Above & Below The Stomach...

Common in advanced PD in ‘off’

- Dysphagia & choking
- Drooling, dry mouth
  - L-dopa – *inconsistent response*
- Abdominal discomfort & bloating - fluctuating
  - suppression of peristalsis in off-state
- Constipation - severe
  → anismus - pelvic floor dysynergia
  → paradoxical striated muscle contraction during defecation
  - can be relieved by apomorphine – *bypassing gut!*

Best Practice - Clinic

GIS questionnaire:

(1) dry mouth
(2) drooling
(3) dysphagia
(4) heartburn
(5) bloating and early satiety
(6) nausea
(7) constipation
(8) defecatory dysfunction

Cersosimo et al, J Neurol 2013
Case 1

- ME 67 yr lady
- 5 years of EPS – all NMS
- Intolerant to L-dopa
- Nausea, bloating, epigastric pain, belching, early satiety
- Constipation
- UUI
- Postural symptoms
- Cognitive decline & visual hallucinations

Trial & Error: Several Specialists

**Gastroenterologist**
- Endoscopy
- H Pylori negative
- ‘IBS’ - working diagnosis
  - Iberogast
  - Dietician
  - OTC supplements

**Neurologist**
- Dose anticipation
- NM offs – akathesia / anxiety / VH / confusion
- Reduced QoL
- Carer stress

**Dietician / CA**
- Constipation

**Geriatrician**
- Rationalization of OTC products
  - Domperidone
  - Intolerant
- Dietary change
  - Neupro patch..bypass gut!
  - SSRI – GI symptoms
  - Donepezil
Case 2

MW – 91 yr lady

- L tremor dominant PD x 6 yrs
- Intolerant - higher dose Madopar
- **Nausea, belching, early satiety, bloating, constipation**
- Dose anticipation
- Motor fluctuations
- Impaired QoL
- Home bound

Reluctant to increase medication

Tolerates

- Madopar 100/25 tds
- Domperidone 10 tds
- Omeprazole 20
- Movicol bd
- CA review

- Neupro patch 2mg...symptom relief!

---

**FIG. 1: Major gastrointestinal problems of patients with PD**

Barichella et al, MDS 2009

Delayed Gastric Emptying in Parkinson's Disease, Marrinan et al, MDS 2014
Gastrointestinal Symptoms (GIS) in PD

- Sialorrhea – 70%
- Dysphagia – 50%
  - Unrelated to severity of PD
  - Asymptomatic aspiration 33%
  - PD medication - dyskinesia
  - Impaired lingual bolus
    - prolonged oral transit time
  - Constipation
    - colon transit time x 2
- Defecatory dysfunction: 67%
  - Pain, sense of incomplete evacuation
- Dyspepsia
  - postprandial bloating
  - abdominal pain
  - early satiety
- Nausea - common
  - gastroparesis
- Constipation
  - L-dopa → nausea & anorexia
- L-dopa
- Madopar – 2 hourly
  - → QID
- Domperidone
- Neupro patch – 12 mg
- Atropine s/l
- Regular botox
  - salivary gland, L biceps
- Sugar free candy
- PPI, Nizatidine – symptom relief
- Movicol
- Prolia, Ca / Vit D

Weight loss – common in women

- Etiology unknown
  - impaired olfaction / taste perception
  - dysphagia
  - Dyskinesias - energy expenditure
- Constipation
- Defecatory dysfunction: 67%
  - Pain, sense of incomplete evacuation
- Rx
  - Sc Apomorphine
  - Botox – sphincter / ms

Case 3

SN – 77 yr lady
- PD x 8 yrs
- Atypical
- L arm dystonia - severe
- Falls – fracture
- Postural symptoms
- Drooling, dyspepsia
- Reflux – intractable, severe despite Rx
- Constipation – troublesome
- Several OTC meds
- Entry to RAC
NZT for DGE

NZT
- Selective H2-receptor antagonist, potent inhibitor of gastric acid secretion
- Prokinetic for gut
- Acetylcholine activity increased:
  - Myenteric plexus → stimulate gastric motility
  - Hypothalamus → ghrelin secretion → gastric motility
- Possible improved jejunal L-dopa absorption
  - improves “delayed-on” & “no-on”

Doi et al, Movement Disorders, 2014

BMI Paradox

- Weight Loss: disease related
  - poor nutritional habits
  - malabsorption
  - cognitive decline – forget to eat
  - hyposmia - less interest in food
  - PD - hypersecretion of insulin & growth hormone – lipolytic state
- Weight gain: therapy related
  - DBS
  - DA – compulsive eating, improved mood
  - PD - abnormal neuroendocrine regulation corticotropin releasing hormone & orexin-related signaling pathways

NUTRITIONAL MANAGEMENT OF PARKINSON’S DISEASE. Barichella et al, MDS 2009
Diet in GIS / PD

A Dynamic Process

Eating Patterns

1. Divide protein equally throughout day
2. Protein redistribution diet (RPD)
   • low-protein breakfast & lunch
   • high-protein dinner

Early PD
• healthy dietary intake
• drug - nutrient interactions

Advanced PD
• Reevaluate
• Personalize diet

Good and bad sides of diet in PD: Kozio et al Nutrition 2013

Low-Protein and Protein-Redistribution Diets for Parkinson's Disease Patients with Motor Fluctuations: A Systematic Review, Cereda et al, MDS 2010

• Elderly
  • consumption of protein and fiber-rich foods limited
    • social factors - isolation, low income
    • disability
    • poor teeth

• Motor fluctuations - recommend PRD

<table>
<thead>
<tr>
<th>TABLE 4. Studies suggesting the features of diet-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source (year)</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Riley et al. (1988)</td>
</tr>
<tr>
<td>Bracco et al. (1991)</td>
</tr>
<tr>
<td>Giménez-Roldán et al. (1991)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
NUTRITIONAL MANAGEMENT OF PARKINSON’S DISEASE  Barichella et al, MDS 2009

NUTRITIONAL MANAGEMENT OF PARKINSON’S DISEASE  Barichella et al, MDS 2009
Case 4

GS 75 yr male
NASH - cirrhosis
Hepatic encephalopathy
Sudden onset EPS
Responsive to Madopar
Keen on weaning
• 3 trials - unsuccessful
Return of tremor / bradykinesia / rigidity

• Continued low dose Madopar x 2 years
• Progression of symptoms
• CRC – hemicolecctiony
• Intractable ascites
• Deceased x 3 months

Acquired Hepatolenticular Degeneration
“Parkinsonism In Cirrhosis”

• Rapidly progressive EPS: 21 %
  • Hypokinesia, dystonia, rigidity
    • Manganese deposition in basal ganglia
      • HE, miners and welders, recreational drug methcathinone, TPN
    • Malfunction of presynaptic manganese transporters
    • Decreased post-synaptic D2 receptors
    • Symmetrical T1 hyperintensities
      • globus pallidus, SN
  • Increased
    • CSF manganese
    • LDopa metabolism → LDopa deficit

Parkinsonism in cirrhosis, R Butterworth, Metab Brain Dis (2013)
Hepatic Encephalopathy & EPS Rx

- L-DOPA works – 50% cases when key players intact
  - Presynaptic / post-synaptic pathways
  - Studies: small / few
  - L-DOPA 3 g/day x 20 weeks *improved symptoms*
    - Gait, tremor
    - Cerebral O2 metabolism = mental status
    - MRI signal hyperintensities
- DA bromocriptine – inadequate studies
- Liver transplant
  - 50% cases EPS improve
  - residual EPS = irreversibility due to neuronal cell loss

*Parkinsonism in cirrhosis, R Butterworth, Metab Brain Dis (2013)*

PD meds & GIS

- Nausea / vomiting common
- Inhibit upper GI motility
  - worsen gastroparesis
- Improve
  - sialorrhea, dysphagia, anorectal dysfunction
- DA
  - excessive weight gain

*STN DBS*
- Improve deglutition /constipation
- Suppress tremor & dyskinesia
  - Weight gain

*Cloud et al, Curr Neurol Neurosci Rep (2011)*
Early PD patients on rotigotine – higher risk of nausea & vomiting

Box. 3 Advantages of Rotigotine

- Improves motor and non-motor symptoms in randomized controlled trials.
- No upper age limit.
- Improves early morning motor symptoms.
- Remains effective for patients with delayed gastric emptying or difficulties swallowing.
- May increase compliance in patients with low compliance to oral medications.

Timpka et al, MOVEMENT DISORDERS CLINICAL PRACTICE 2016

Neural Control of the Gastrointestinal Tract: Implications for Parkinson Disease, Cerosimo et al, MDS 2008
Brain Gut Axis

- **Gastric emptying**
  - Extrinsic: vagal and splanchnic pathways
  - Intrinsic: ENS in entire gut ‘second brain’
    - 2 plexuses:
      - Submucosal Meissner’s plexus
      - Myenteric Auerbach’s plexus
    - connects with vagus in stomach ‘brain gut axis’
    - Vagal damage - delayed gastric emptying

- **Neuroendocrine mediators**
  - ghrelin and motilin - accelerate emptying
  - CCK, GLP-1, and PYY - delay emptying
The Role of Small Intestinal Bacterial Overgrowth in Parkinson's Disease, Fasano et al, Movement Disorders, 2013

- **SIBO**
- motor fluctuations
- eradication HP infection
- meaningful clinical effect
Ghrelin & Gut Motility

Ghrelin
- Peripheral
  - Prokinetic
- central
  - enhances appetite
- key orexigenic hormone
  - peak – fasting
  - rapid decline – food intake

- Therapy of DGE / Gastroparesis
- Limited options
- Investigational
  - Motilin / ghrelin agonists

Marrinan et al, MDS 2014

Treating ‘OFF’

Apopomorphine injections
- Dose failures in advanced PD - time-to-ON >60 minutes
  - more common with levodopa vs apomorphine (46% vs. 7%).
  - >40% of patients had at least one “dose failure” / week
- Common AEs were nausea and dizziness
- Usually well tolerated

Sublingual Apomorphine
- 40% - 6 yrs Rx
- 90% - 9 yrs Rx
- Wearing OFF: impacts QoL
  - 2/3 cases – “waiting to turn ON”
- SL Apomorphine
  - Full ON: 15 / 19 cases for >90 mins
  - Time to efficacy 15 – 30 mins

Hauser et al, MDS 2016
Innovations In Therapy

Conventional formulations of L-dopa

• Irregular absorption & rapid catabolism
• Optimal dosing regimens can vary greatly in PD patients
• Variable interplay of SDR, LDR (short / long duration response)
• IR formulation not the best
• Sinemet CR, Madopar HBS, Stalevo – inconsistent response
• LCIG PEJ delivery - not practical option for all

New formulations on the horizon:

• oral CD—L-dopa formulation, L-dopa pro-drugs, gastric-retentive SR
• L-dopa, inhaled L-dopa, sc infusion - solubilized CD L-dopa

LeWitt et al, MDS2015

Time To Reflect

Thank you!