Gastrointestinal pathology in Parkinson's disease

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Introduction

- Gastrointestinal dysfunction is an important nonmotor feature of Parkinson disease that affects patients' quality of life from the early to late stages of PD .

- Common symptoms include:
  - ❖Constipation
  - ❖ nausea and vomiting
  - ❖ gastric paresis
  - ❖ dysphagia
  - ❖Sialorrhea
  - ❖appetite loss

- Approximately one to three quarters of the PD population have at least one GI symptom.

Pathophysiology

- Dopaminergic deficiency secondary to nigrostriatal damage may be responsible for some aspects of GI dysfunction in PD.

- Additional sites of involvement, both within the central nervous system and beyond it, also play important roles.

- The dorsal motor nucleus of the vagus (DMV), which provides parasympathetic innervation to much of the GI tract, is one of the earliest sites of pathology within the CNS in PD.

Pathophysiology

- Extensive involvement of the ENS is also present.
- Lewy bodies identified within the ENS at multiple levels .
- ENS involvement in PD certainly includes dopaminergic neurons but other neuronal systems within the gut are also affected .

Enteric Nervous System

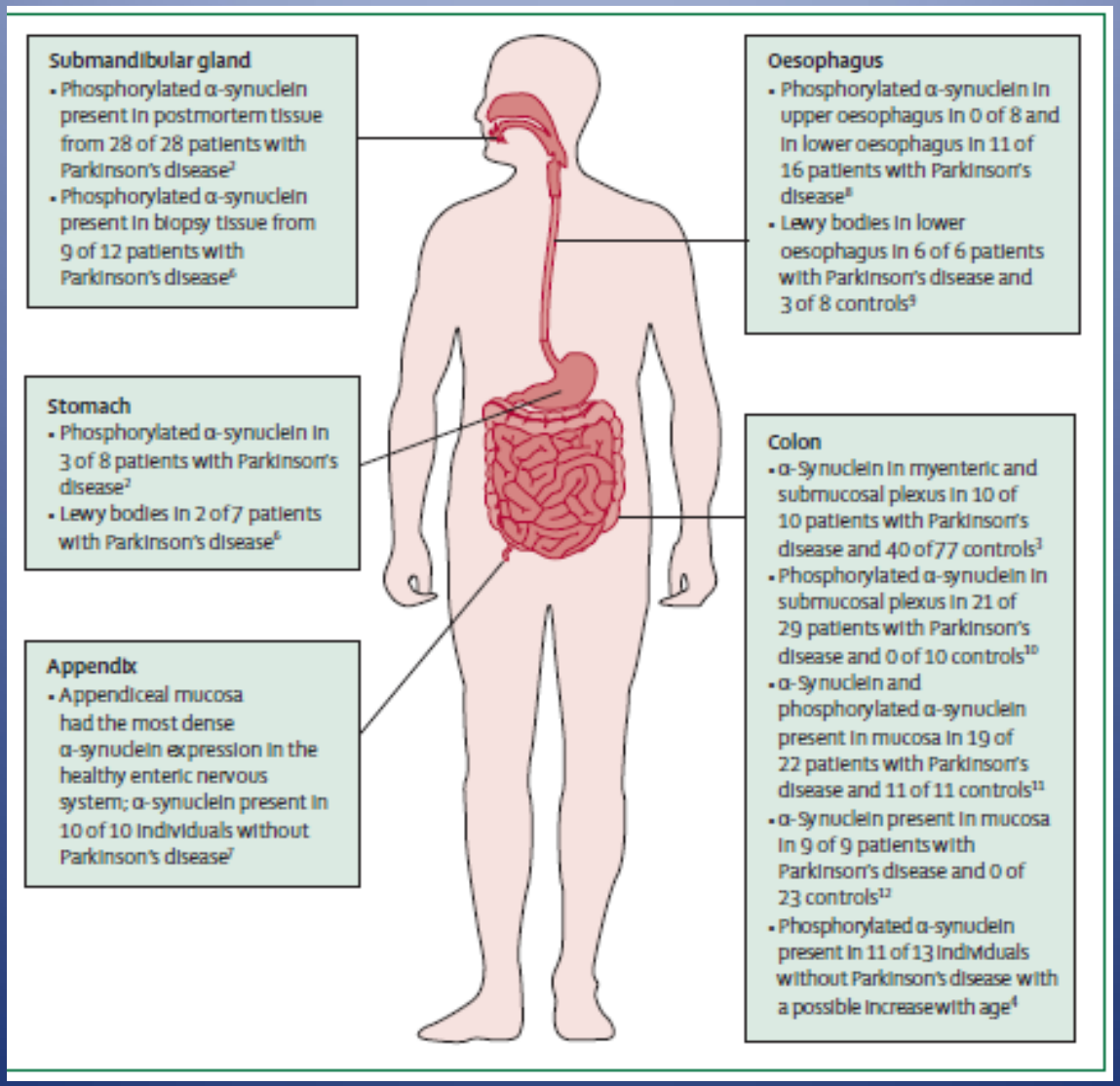
The ENS controls motility, mucosal secretion and absorption, mucosal growth, local blood flow and the immune function in the gut

Synucleinopathy in the gastrointestinal tract

- The pathological changes of Parkinson's disease are defined by abnormal α-synuclein accumulation in the brain in characteristic Lewy bodies or Lewy neurites.

- Evidence for abnormal α-synuclein accumulation outside the brain, including throughout the enteric nervous system, is growing.

Distribution of α-synuclein and phosphorylated α-synuclein in the enteric nervous system in patients with Parkinson's disease



Synucleinopathy

- α-Synuclein deposition occurs in the myenteric and submucosal plexuses and mucosal nerve fibers.

- The highest concentrations of enteric phosphorylated α-synuclein is in the submandibular gland and lower esophagus, lower concentrations in the stomach and small intestine, and lowest concentrations in the colon and rectum.

Synucleinopathy

- The distribution of synucleinopathy is associated with gastrointestinal symptoms along the entire gastrointestinal tract.

- The extent of gastrointestinal dysfunction, with corresponding widespread enteric nervous system synucleinopathy, suggests that a disruption in the physiological function of α-synuclein might have a role in gastrointestinal dysfunction.

ENT as the origin of PD

- The hypothesis that Parkinson's disease might arise from the gut was posited a decade ago.
- Several studies have suggested that the pathological progression of PD might be mediated by the prion-like properties of α-synuclein.
- The enteric nervous system is affected early and the dense innervation originating from the DMV might provide a conduit for abnormal forms of α-synuclein to access the CNS.

ENT as the origin of PD

- The appendiceal mucosa also has been proposed as a potential site of entry of α-synuclein because this region has the highest expression of α-synuclein in ENS in healthy individuals.

- Other hypothesis relates to the finding of increased aggregated α-synuclein in the colon of control individuals.

- It is possible that in PD, α-synuclein might disaggregate and infiltrate the CNS as soluble α-synuclein oligomers.

Gastrointestinal Pathology

Constipation

Constipation

Definition

Rome III criteria:

1. Must include *two or more* of the following:
   a. Straining during at least 25% of defecations
   b. Lumpy or hard stools in at least 25% of defecations
   c. Sensation of incomplete evacuation for at least 25% of defecations
   d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
   e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
   f. Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Patient's Complaints

- Straining 52%
- Hard stools 44%
- Inability to defecate at will 34%
- Infrequent defecation 32%

Classification

Functional

Secondary

Secondary causes

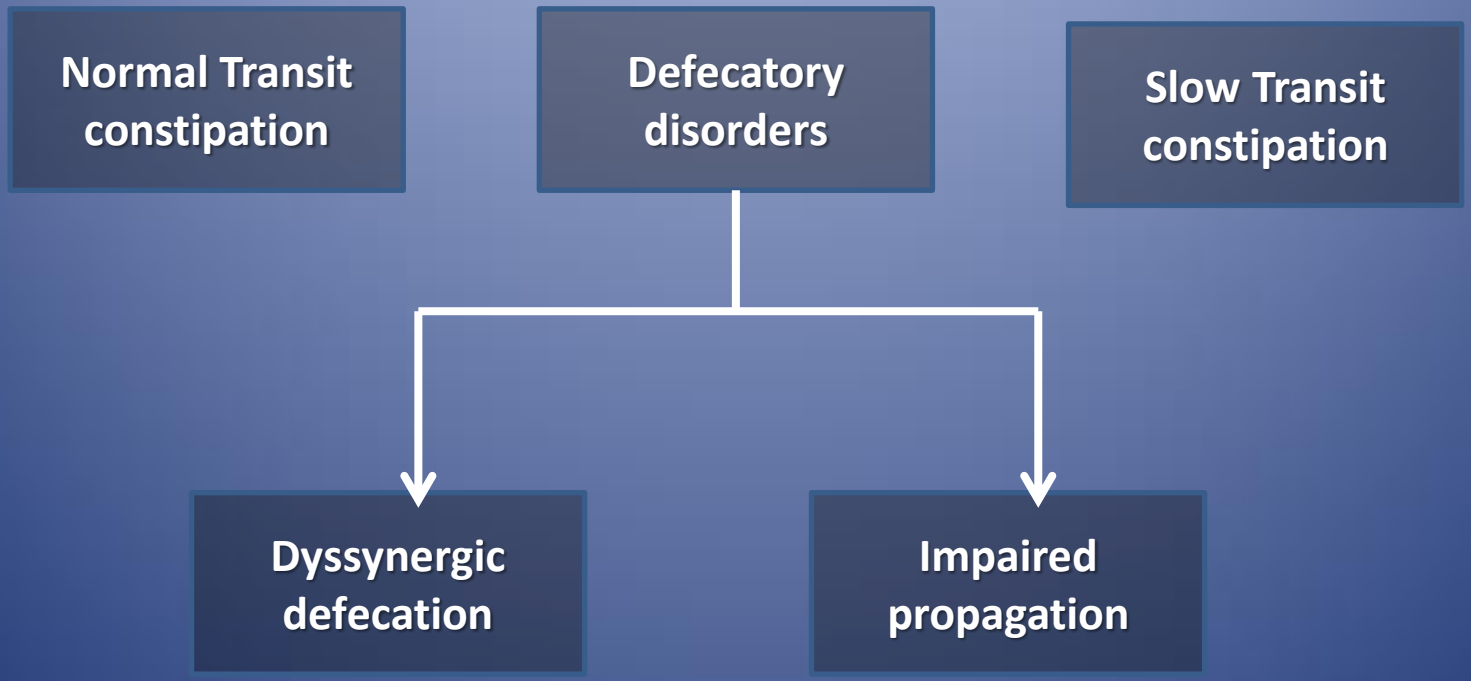
Mechanical Obstruction
Anal stenosis
Colorectal cancer
Extrinsic compression
Rectocele or sigmoidocele
Stricture

Medications
Antacids
Anticholinergic agents (e.g., antiparkinsonian drugs, antipsychotics, antispasmodics, tricyclic antidepressants)
Anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin)
Antineoplastic agents (e.g., vinca derivatives)
Calcium channel blockers (e.g., verapamil)
Diuretics (e.g., furosemide)
5-Hydroxytryptamine$_3$ antagonists (e.g., alosetron)
Iron supplements
Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen)
Mu-opioid agonists (e.g., fentanyl, loperamide, morphine)

Metabolic and Endocrinologic Disorders
Diabetes mellitus
Heavy metal poisoning (e.g., arsenic, lead, mercury)
Hypercalcemia
Hyperthyroidism
Hypokalemia
Hypothyroidism
Panhypopituitarism
Pheochromocytoma
Porphyria
Pregnancy

Neurologic and Myopathic Disorders
Amyloidosis
Autonomic neuropathy
Chagas' disease
Dermatomyositis
Intestinal pseudo-obstruction
Multiple sclerosis
Parkinsonism
Progressive systemic sclerosis
Shy-Drager syndrome
Spinal cord injury
Stroke

Functional Constipation



Normal Transit Constipation

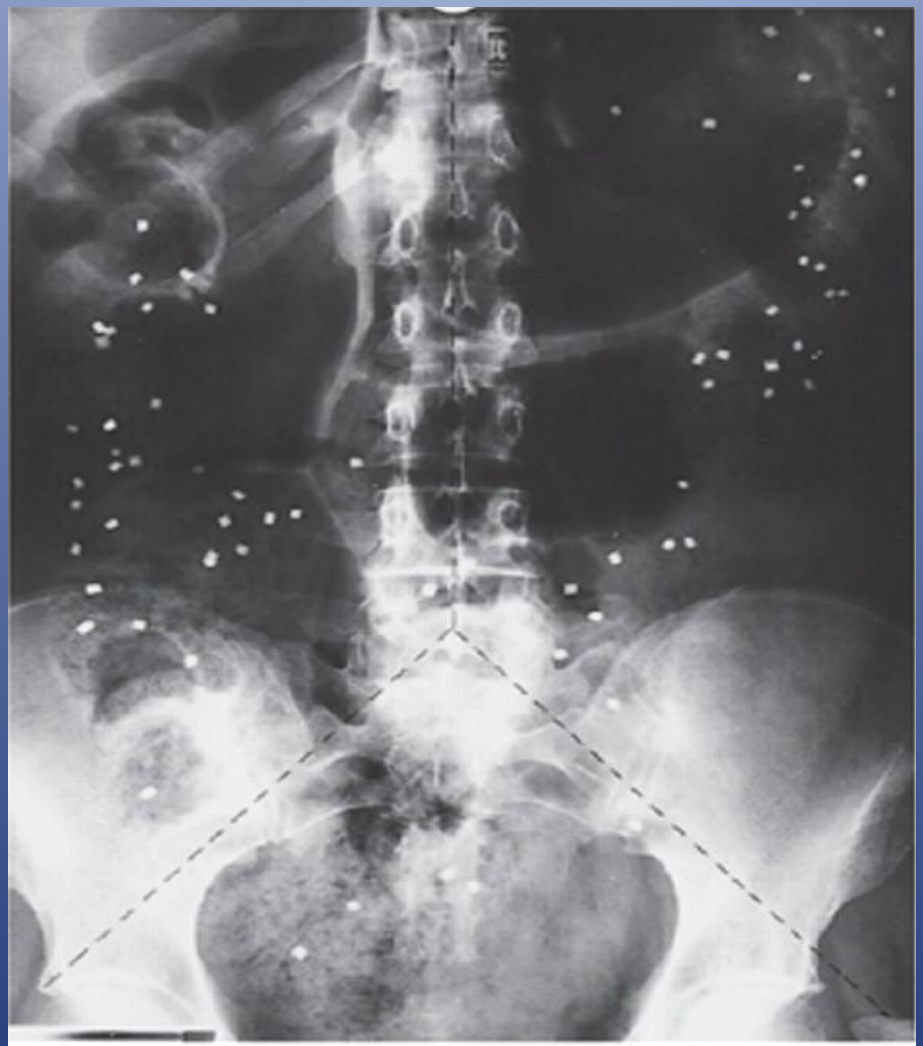
- Stool travels along the colon at a normal rate.
- Patients may have :

  misperceptions about their bowel frequencies

  psychosocial distress

  abnormalities of anorectal sensory and motor function
- Most patients have normal physiologic testing.
- Overlap with IBS-C: abdominal pain is the predominant symptom in IBS

Slow Transit Constipation



(a)

Defecatory Disorders

- Arise from failure to empty the rectum effectively because of an inability to coordinate the abdominal, rectoanal, and pelvic floor muscles:

  Impaired rectal contraction (61%)

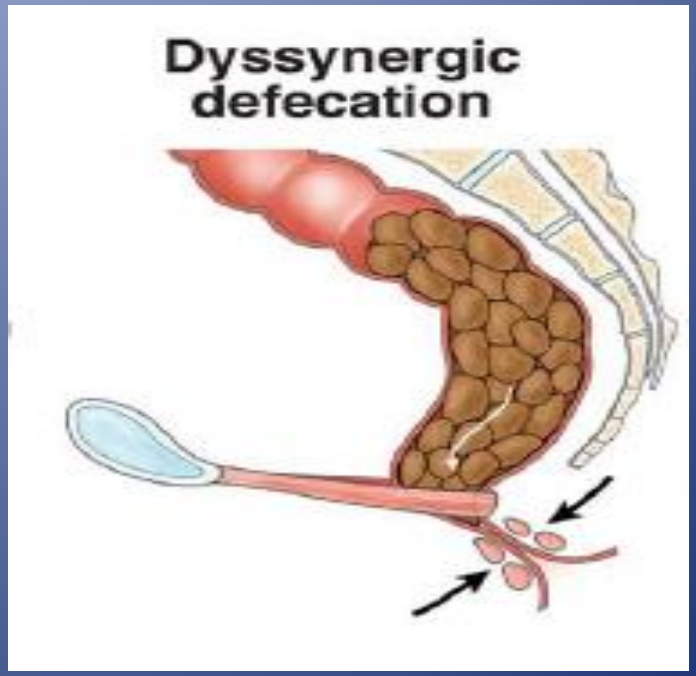
  Paradoxical anal contraction (78%)

  Inadequate anal relaxation

- 50% - 60% also demonstrate an impaired rectal sensation

Dyssynergic defecation

EAS and puborectalis contract during defecation



Incidence of PD according to bowel movements

Bowel movements/d	Sample size	Incident PD cases	Incidence, rate/10,000 person-years	
			Unadjusted	Age-adjusted
<1	289	10	19.6	18.9
1	4371	66	8.0	7.9
2	1704	17	5.2	5.4
>2	426	3	3.8	3.9
Test for trend	—	—	$p = 0.002$	$p = 0.005$
Overall	6790	96	7.5	—

Abbott RD et al. Neurology 2001

Constipation and PD

- Autopsy studies on subjects with no clinical signs of parkinsonism found:
  - ❖ late life constipation is associated with incidental Lewy bodies in the substantia nigra and locus caeruleus
  - ❖ decreased substantia nigra neuron density
- These clinical and pathologic findings suggest that constipation may in some cases represent incipient PD.

Abbott RD et al. Neurology 2001
Abbott RD, et al.Mov Disord 2007

Constipation and PD

- Prevalence: > 50% of PD
- Constipation often occurs early in the disease course and may predate motor features by several years
- The mechanisms are diverse:
  - Slow transit: CTT> 2 norm
  - Dyssynergic defecation
  - Drug adverse effect

Edwards Let al. Mov Disord. 1993
Abbott RD, et al. Neurology. 2001.

Dyssynergic defecation

- Difficulty with the act of defecation, resulting in excessive straining, pain, and incomplete evacuation> 2/3 of individuals with PD.

- Documented abnormalities in the defecation process in PD patients:
  - ❖ Paradoxical contraction of the puborectalis
  - ❖ Paradoxical contraction external anal sphincter

Edwards LL, et al. Mov Disord 1991

Drug Side effects

- Constipation is a common adverse effect of many Parkinson's disease drugs, particularly anticholinergics and dopamine agonists.

Evaluation

- Colonoscopy in > 50 years or hazard signs.

- Thorough history and digital rectal examination is helpful to differentiate colonic transit abnormality versus dyssynergic defecation.

Possible Techniques For Functional Assessment

Investigation	Modality Assessed	Clinical Use
Anorectal manometry	(1) Anal sphincter function	Established, limited value
Traditional	(2) Rectoanal reflexes	Established, limited value
	(3) Rectal sensation (balloon)	Established
	(4) Rectal compliance	Established, limited value
	(5) Defecatory maneuvers	Established
	(6) Saline continence test	Obsolete
High resolution	See (1, 2, and 5 above)	Research
Vector volume	Anal sphincter function, pressure profile	Obsolete
Prolonged ambulatory	Anorectal/rectosigmoid motility	Research
Perineometer	Pelvic floor descent	Obsolete
Perineal dynamometer	Puborectalis function	Research
Barostat studies	(1) Rectal sensation	Established
	(2) Rectal compliance	Established
	(3) Rectal tone, tension	Research
	(4) Rectal capacity	Research
	(5) Rectal motility	Research
Impedance planimetry	Rectal biomechanical properties	Research
Endoanal ultrasound	Two-dimensional imaging of the anal sphincters	Established
	Three-dimensional imaging of the anal sphincters	Research
Endoanal MRI	Imaging of the anal sphincters	Research
Neurophysiologic		
Nerve conduction	Pudendal nerve terminal motor latency	Established, limited value
Electromyography	(1) Motor unit action potentials	Established, limited value
	(2) Fiber density	Established, limited value
	(3) Jitter	Research
Evoked potentials	(1) Motor	Research
	(2) Somatosensory	Research
Other	Anocutaneous reflex	Established, limited value
	Strength-duration test	Research
Anorectal sensation		
Electrostimulation	(1) Mucosal electrosensitivity	Established, limited value
Thermal stimulation	(2) Mucosal thermosensitivity	Research
Rectal evacuation		
Balloon expulsion test	Rectal evacuatory function	Established
Evacuation proctography	Rectal evacuatory function	Established
Scintigraphic proctography	Rectal evacuatory function	Obsolete
Dynamic MRI proctography	Rectal evacuatory function, pelvic organ movement	Research
Colonic transit studies		
Radiopaque markers	Global colonic transit	Established
Scintigraphy	Segmental colonic transit	Established, limited value

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Anorectal Manometry

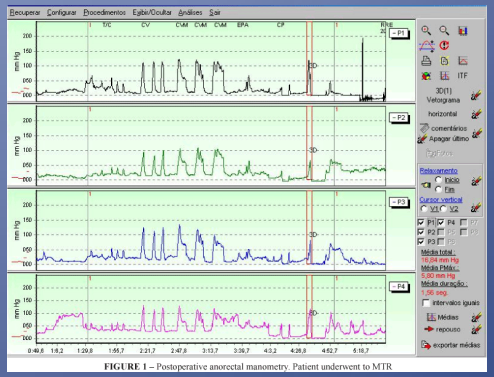
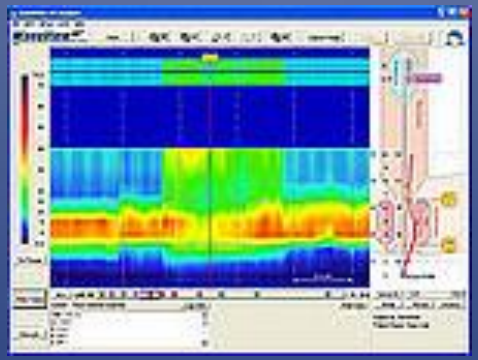
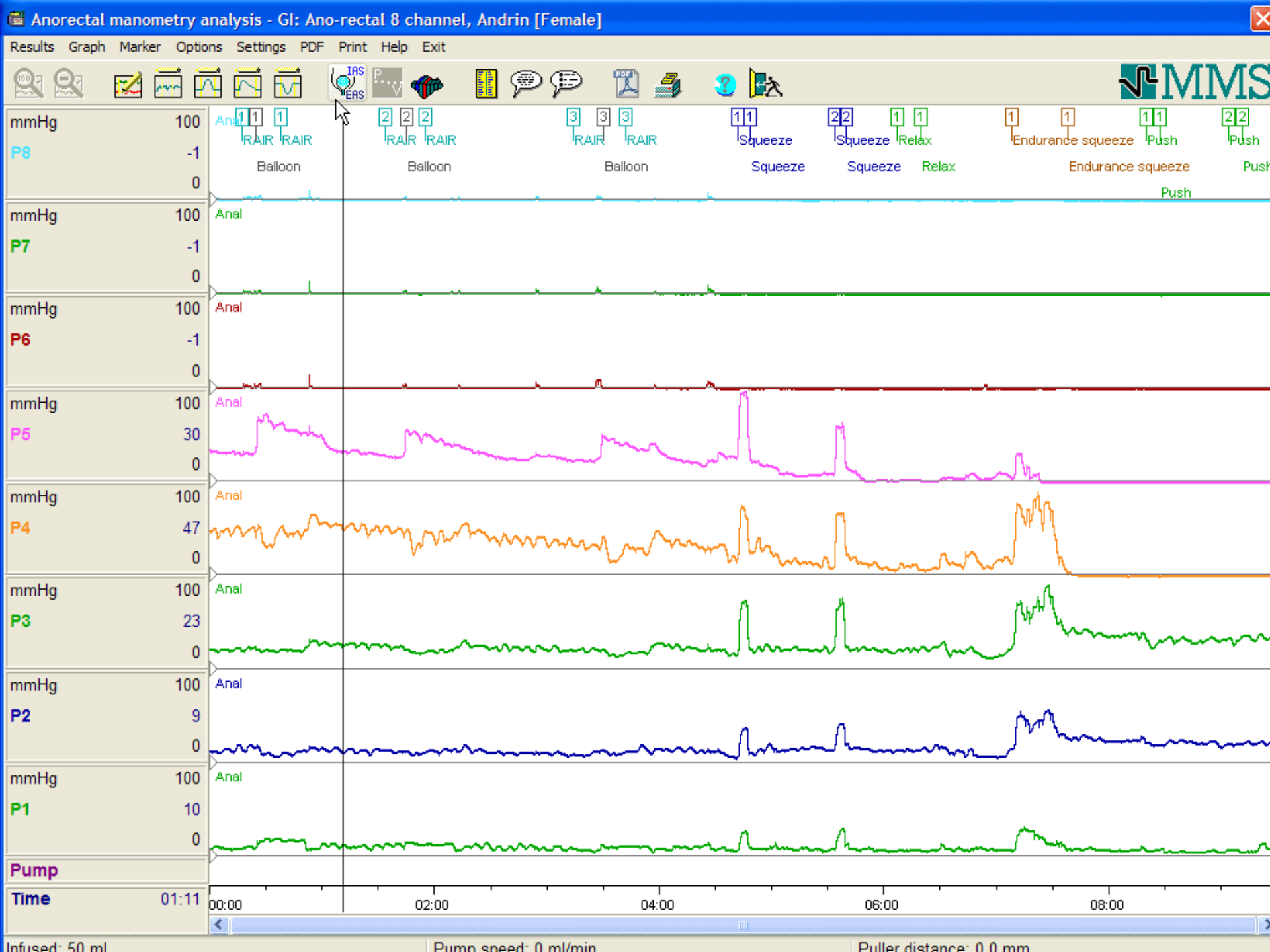


FIGURE 1 – Postoperative anorectal manometry. Patient underwent to MTR



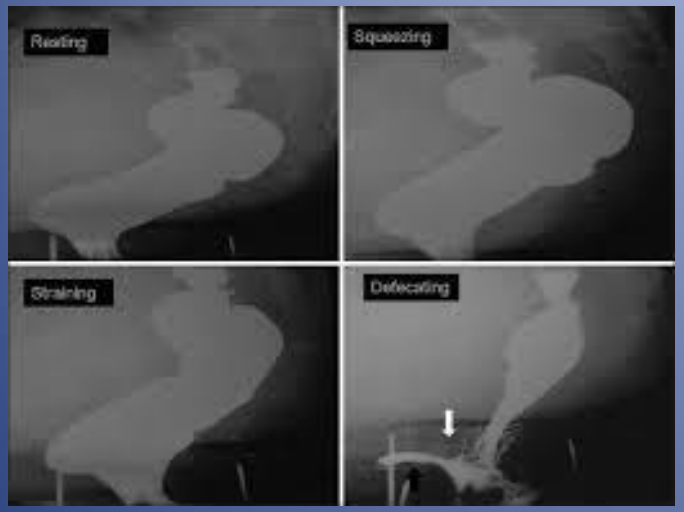
Pull Through Anorectal Manometry

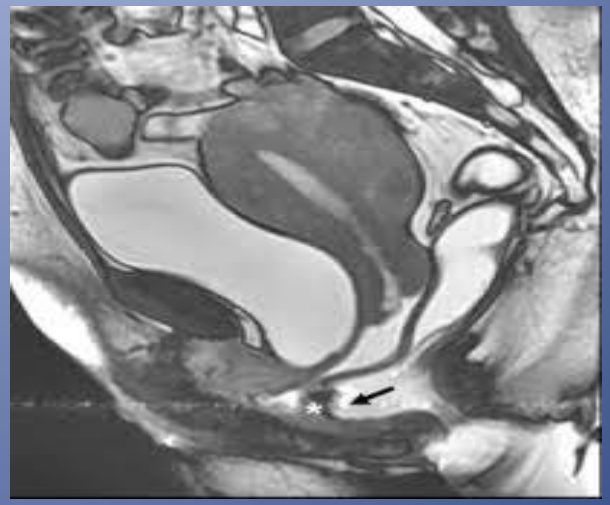

Anorectal manometry analysis - GI: Ano-rectal 8 channel, Andrin [Female]
Results Graph Marker Options Settings PDF Print Help Exit
MMS
mmHg 100 P8 -1 0
mmHg 100 P7 -1 0
mmHg 100 P6 -1 0
mmHg 100 P5 30 0
mmHg 100 P4 47 0
mmHg 100 P3 23 0
mmHg 100 P2 9 0
mmHg 100 P1 10 0
Pump
Time 01:11
Anal
RAIR
Balloon
Squeeze
Relax
Endurance squeeze
Push
00:00
02:00
04:00
06:00
08:00
Infused: 50 ml
Pump speed: 0 ml/min
Puller distance: 0.0 mm

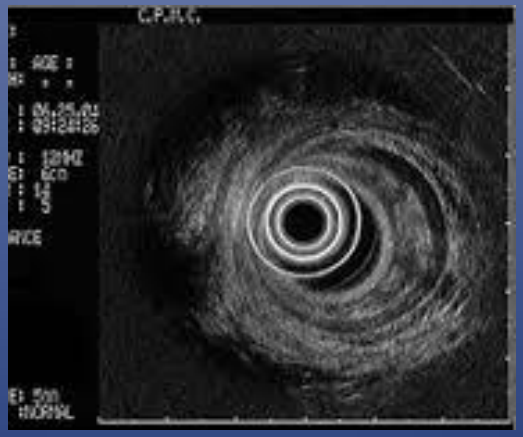
Colon Transit Time

Defecography

Defecography







Evaluation

- The usefulness of the radio-opaque marker study for colonic transit measurement, and of anorectal manometry, the balloon expulsion test, and defecography have not been validated in patients with PD.

Treatment of constipation in PD

- Trials assessing efficacy of various drugs have been scarce.

- Results from an open-label observational study in ten patients with Parkinson's disease showed that an macrogol 3350 was efficacious.

TABLE 1. *Clinical data of PD and MSA patients before and after macrogol treatment*

Patient no.	Age (yr)	Gender	Stool freq. before macrogol 3350	Treatment before macrogol	Duration of treatment (wk)	Maintenance macrogol dose	Stool freq. (per wk)	Softening of stool change*	Effect on ease of defecation change*	Global impression change*
PD										
1	75	F	1 per 2 wks	Lactulose, senna, domperidone	21	2 × 1 bag/day	4	3	3	3
2	76	M	1 per wk	Lactulose, domperidone, picosulfate, senna, clyster	9	1 × 1 bag/day	4	3	3	3
3	66	M	2 per wk	Lactulose, cisapride	15	2 × 1 bag/day	3	2	3	3
4	70	F	<1 per wk; coprostasis	Lactulose	11	1 × 1 bag/2nd day	3	3	3	3
5	74	F	1 per wk		15	1 × 1 bag/2nd day	7	3	3	3
6	57	M	<1 per wk	Lactulose	9	2 × 1 bag/day	3	3	3	3
7	60	M	1 per wk	Lactulose	13	1 × 1 bag/day	4	3	3	3
8	67	M	1 per wk	Lactulose	11	1 × 1 bag/3rd. day	4	3	3	3
MSA										
1	62	F	1 per wk or less	Cisapride, lactulose	10	2 × 1 bag/day	4	3	3	3
2	51	F	1 per wk or less	Cisapride, lactulose	10	2 × 1 bag/day	4	3	3	3

*Change: 0, no difference; 1, slight improvement; 2, moderate improvement; 3, marked improvement.
Freq, frequency

Eichhorn T, Oertel W. Mov Disord 2001.

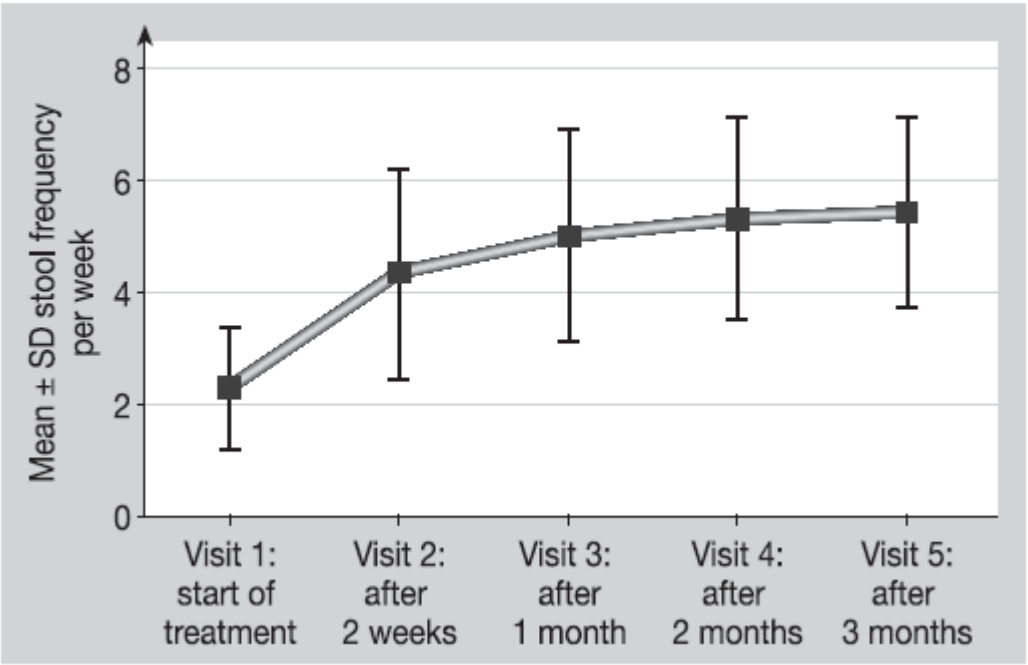
Efficacy and tolerability of PEG 3350 plus electrolytes (Movicol®) in chronic constipation associated with Parkinson's disease

H.-J. Gruss[1], G. Ulm[2]

- A non-interventional, post-marketing study with a follow-up period of 12 weeks.

- 544 evaluable patients (50 % female and a mean age of 73 ± 9 years) received commercially available PEG 3350 plus electrolytes.

EurJGer 2004



The mean number of successful defecations increased from 2.3 ± 1.1 per week (pre-treatment) to 5.3 ± 1.8 per week (after eight weeks), and this improvement was maintained throughout the remaining study

- The proportion of patients achieving two or less successful defecations per week fell from 69 % at baseline to 5 % or less from eight weeks onwards.

- Improvements were also seen for consistency of stools, flatulence, stomach pain and bloating.

- After three months the bowel function of 64 % of patients was rated as having normalised and as clearly improved in a further 34 % of patients.

Placebo-controlled trial of lubiprostone for constipation associated with Parkinson disease

- Lubiprostone is a chloride channel activator with FDA approval for the management of IBS-C and chronic constipation.
- Double-blind, randomized, controlled study
- After enrollment, patients were initially followed for 2 weeks and then were randomly assigned 1:1 to lubiprostone, and the dose was titrated up to 48 g/day.
- They returned 4 weeks later for a final assessment.

Ondo WG. Neurology 2012

Item	Lubiprostone (n = 25)	Placebo (n = 27)	*p* Value
Patient subjective assessment of change, n			0.001; $z = 3.188$
Mildly worse	1	4	
No change	3	12	
Mildly improved	6	6	
Much improved	9	3	
Very much improved	7	2	
Visual analog scale score (change in constipation) visit 2 to visit 3	51.4 ± 8.5 to 71.2 ± 16.6	50.7 ± 5.9 to 56.8 ± 13.0	0.001
BM review questionnaire, visit 2 to visit 3	13.3± 4.91 to 6.6 ± 1.11	13.4 ± 4.8 to 10.2 ± 6.5	0.033
BM diaries BMs/day for period before to after drug	0.75 ± 0.80 to 0.97 ± 0.88	0.84 ± 0.76 to 0.83 ± 0.76	0.001
Weight change: change visit 2 to visit 3 (pounds)	−0.32 ± 2.39	−1.01 ± 3.56	0.440
UPDRS part II, "on": change visit 2 to visit 3	−0.48 ± 3.31	0.54 ± 4.26	0.352
UPDRS part II "off" change visit 2 to visit 3	0.04 ± 0.45	1.13 ± 5.41	0.323
UPDRS part III, with medications: change visit 2 to visit 3	−0.16 ± 5.70	1.58 ± 6.31	0.315

- A marked or very marked clinical global improvement was reported by 64.0% of subjects receiving 18.5% subjects receiving placebo ($p<0.001$).

- The constipation rating scale ($p<0.05$) and stools per day ($p <0.001$) all improved with drug compared with placebo.

Dyssenergic Defecation

- The usefulness of biofeedback training has not been specifically evaluated in PD patients.
- Botulinum toxin injections into the puborectalis muscle produced improvement in over 50% of PD patients, with improvement typically persisting for several months.
- Improvement in defecatory dysfunction has been reported to occur after subcutaneous injection of the dopamine agonist apomorphine

Edwards LL, et al. Ann Neurol. 1993.
Albanese A, et al. Mov Disord. 1997

Dysphagia

Dysphagia

Dysphagia

- The prevalence is 30-80%.
- Some investigators suggest that dysphagia may be present early in the course of PD, occasionally even the presenting clinical feature.
- All stages of swallowing :oral, pharyngeal, and esophageal may be affected.

Dysphagia

- **Oral Stage:**

➢ Rigidity, bradykinesia, and tremor of the tongue and oral musculature may impede bolus formation.

- **Pharyngeal Stage:**

➢ Pharyngeal dysmotility may result in misdirected swallows, which increase the risk of aspiration.

➢ Cricopharyngeal muscle dysfunction in the form of impaired relaxation may further impede swallowing.

Dysphagia

- **Esophageal dysfunction:**

➢ Various manometric studies demonstrate esophageal dysfunction in 60-70% of PD patients.

Aspiration

- Pharyngeal dysfunction and oropharyngeal transit abnormalities increase the risk of aspiration.

- Aspiration is present in 15–56% of patients with Parkinson's disease and silent aspiration in 15–33% of patients.

Pathophysiology

- Oropharyngeal dysphagia is often attributed to bradykinesia and rigidity secondary to basal ganglia dysfunction.

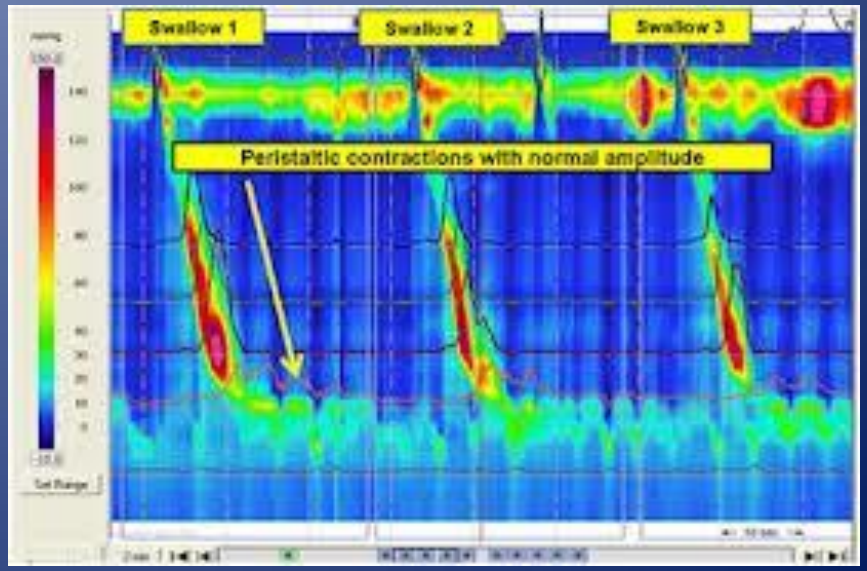
- Peripheral mechanisms that include motor and sensory pharyngeal nerves might also play a part.

Evaluation

- Patients with and dysphagia should be considered for assessment of both oropharyngeal and esophageal dysphagia, guided by clinical history and presentations.
- **Videofluoroscopy** is the gold standard in the assessment of oropharyngeal dysfunction in patients with Parkinson's disease.
- **Esophageal manometry** study is the most accurate and sensitive test to identify esophageal dysmotility

Videofluroscopy

Esophageal Manometry



Evaluation

- In patients who are unable to tolerate an esophageal manometry study, barium swallow can be used.
- Endoscopy should be considered if structural or inflammatory lesions are suspected.

Treatment

- No universally effective treatment approach for dysphagia in PD has been identified.
- **Dopaminergic medication:** responsiveness in only a minority of patients.
- **Non-pharmacologic techniques**: chin-down swallowing and use of thickened liquids may be useful for some individuals.
- **Impaired cricopharyngeal relaxation** can be ameliorated either by surgical myotomy or botulinum toxin injection.
- **PEG placement** in severe, intractable dysphagia

Gastroparesis

Gastroparesis

- Prevalence of gastroparesis in PD is 70% to 100%, although not all affected individuals have symptoms.

- Gastroparesis can be present in both early and advanced Parkinson's disease, with delays in gastric emptying more likely to be associated with solid meals.

Gastroparesis

- Nausea, vomiting, early satiety, excessive fullness, bloating, and abdominal distension characterise gastroparesis.

- Because levodopa is absorbed in the small intestine, gastroparesis might result in delayed or complete loss of benefit of the levodopa dose.

Pathophysiology

- Both central and enteric components.
- The DMV is involved early in the course of disease .
- Involvement of the enteric nervous system might occur even earlier in Parkinson's disease.
- Abnormal ghrelin function might also be implicated in gastroparesis in Parkinson's disease.

Evaluation

- Scintigraphic methods are employed most frequently to measure gastric emptying during the course of 4 h with a standard meal labelled with Technetium-99.

- 13C-sodium octanoate breath test.

Treatment

- Treatment of gastroparesis in Parkinson's disease is challenging because levodopa might delay gastric emptying.

- Prokinetic therapy should be considered to improve gastric emptying and gastroparesis Symptoms.

Dopamine antagonists

- Metoclopramide- contraindicated
- Domperidone (Motilium)

5-HT4 receptor agonists

- Cisapride and Tegaserod- effective, but have been withdrawn from the market because of cardiotoxic effects.

- Prucalopride is a newer 5-HT4 agonist with no documented cardiotoxic effects. Its usefulness in gastroparesis has not been investigated.

Motilin Agonists

- Erythromycin, although effective, is not suitable for chronic use owing to drug interactions and QT prolongation.
- Azithromycin might be a preferable alternative
- Over longer periods these agents are often associated with tachyphylaxis due to downregulation of the motilin receptor.
- Clinical responsiveness drops after 4 weeks of oral erythromycin.

Janssens J, et al. N Engl J Med 1990.
Richards RD, et al.. Am J Gastroenterol 1993

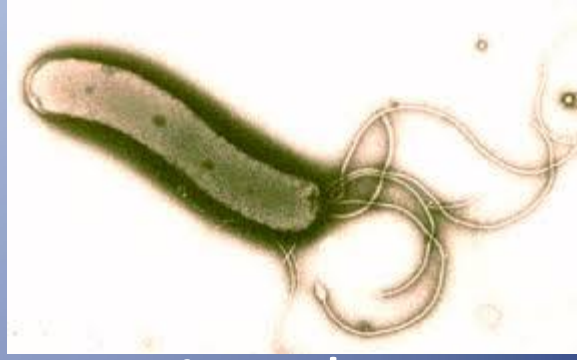
Other Therapy Modalities

- Botulinum neurotoxin injections into the pyloric sphincter:
  - Anecdotally reported to ameliorate gastroparesis in patients with PD.
  - Extensive investigation in patients without Parkinson's disease but with gastroparesis has not shown a clear benefit.
- Improvement in gastric emptying after DBS of the subthalamic nucleus has been reported.

Other Therapy Modalities

- Gastric electrical stimulation might be effective in refractory cases, although not studied in patients with PD.

Helicobacter Pylori



- A diagnosis of H pylori gastritis was associated with about a 45% increased risk of PD in a population based study.
- The peripheral immune response, triggered by H pylori, might disrupt the BBB, thus promoting microglia-mediated inflammation and autoimmune neurotoxic effects.
- However, the prevalence of H pylori in PD is similar to that in the general population.

Nielsen HH, et al.. Eur J Neurol 2012.

Helicobacter Pylori

- Strong evidence exists for a biological contribution of H pylori to motor fluctuations in PD, owing to interference in the absorption of levodopa.

- H pylori infection was associated with an increased delay in onset of action of levodopa and decreased on-time (time during which symptoms are adequately controlled).

Nielsen HH, Eur J Neurol 2012
Narozanska E, Clin Neuropharmacol 2014.

Helicobacter Pylori

- Non-invasive tests for H pylori infection include the urea breath test, the stool antigen test, and serological tests.
- The effect of H pylori eradication on motor fluctuations has been confirmed in a double-blind Study.
- The improvement was greater after 3 months than in shorter-term follow-up, suggesting a time-dependent decrease in H pylori-related inflammatory changes in gastrointestinal mucosa.

Lee WY, Mov Disord 2008
Pierantozzi M, Neurology 2006;.

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth

- Prevalence of SIBO in patients with PD was found to be as high as 55% (vs 20% in healthy controls).

- Patients with SIBO have been reported to have more severe motor fluctuations (off - time, delayed on-time, and no on-time) than those without SIBO.

Scheperjans F, et al Mov Disord 2015

Evaluation

- The gold standard for the diagnosis of SIBO is colony counts of cultured jejunal aspirate, but this method is invasive and its diagnostic reliability is highly variable.

- The lactulose breath test and the glucose breath test, measuring breath hydrogen after oral administration of lactulose or glucose, are widely used .

Treatment

- Many different antibiotic regimens have been advocated for SIBO, including ciprofloxacin, metronidazole, neomycin, norfloxacin, and doxycycline.
- The common antibiotic treatment cycle is 1–2 weeks every 1–3 months based on clinical response.
- When available, rifaximin has the most favourable tolerability.

Malnutrition

Malnutrition

- The prevalence of malnutrition in Parkinson's disease ranges up to 24%.

- Malnutrition is an established determinant of health in elderly people and is linked to reduced functional ability, quality of life, and survival in patients with PD.

Pathophysiology

- Motor impairment (dysphagia)
- Fear of increased off –time
- Fasting associated with drug administration
- Drug-induced nausea
- Dyskinesias contribute to weight loss by increasing energy expenditure, and low bodyweight is associated with an increased risk of dyskinesias.

Pathophysiology

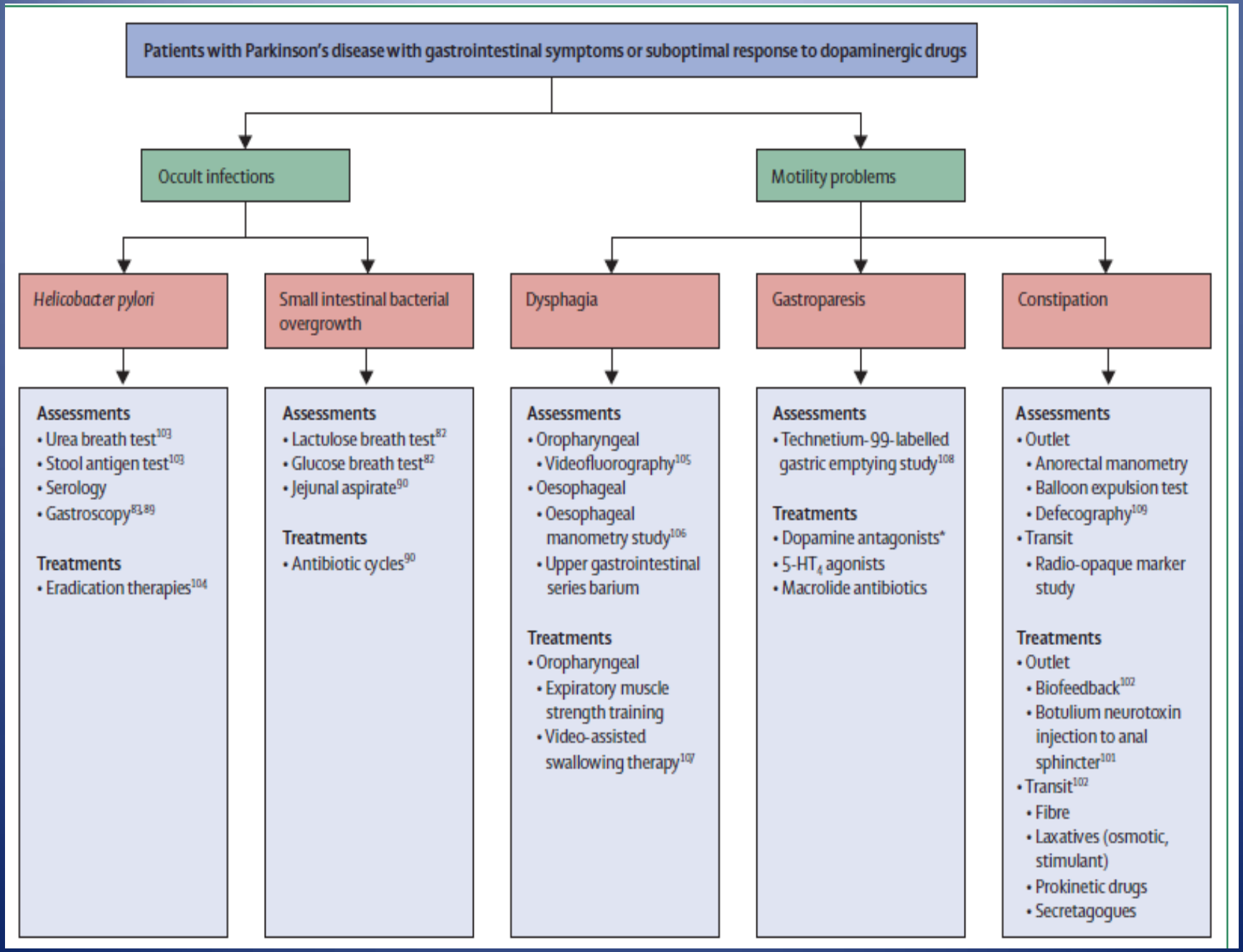
- Administration of levodopa has been associated with impaired nutritional state.
- A cumulative levodopa dose is purportedly associated with nutritional deficiency through changes in homocysteine, vitamin B6, and B12 levels.
- A direct effect of levodopa on fat metabolism, skeletal muscle glucose uptake, and hormones has also been postulated.

Treatment

- For patients with Parkinson's disease who have substantial or persisting weight loss, assessment for an alternative medical cause should be undertaken.

- Nutritional intervention might contribute to improved quality of life.

Summary


Patients with Parkinson's disease with gastrointestinal symptoms or suboptimal response to dopaminergic drugs
Occult infections
Motility problems
Helicobacter pylori
Small intestinal bacterial overgrowth
Dysphagia
Gastroparesis
Constipation
Assessments
• Urea breath test[103]
• Stool antigen test[103]
• Serology
• Gastroscopy[83,89]
Treatments
• Eradication therapies[104]
Assessments
• Lactulose breath test[82]
• Glucose breath test[82]
• Jejunal aspirate[90]
Treatments
• Antibiotic cycles[90]
Assessments
• Oropharyngeal
• Videofluorography[105]
• Oesophageal
• Oesophageal manometry study[106]
• Upper gastrointestinal series barium
Treatments
• Oropharyngeal
• Expiratory muscle strength training
• Video-assisted swallowing therapy[107]
Assessments
• Technetium-99-labelled gastric emptying study[108]
Treatments
• Dopamine antagonists*
• 5-HT4 agonists
• Macrolide antibiotics
Assessments
• Outlet
• Anorectal manometry
• Balloon expulsion test
• Defecography[109]
• Transit
• Radio-opaque marker study
Treatments
• Outlet
• Biofeedback[102]
• Botulium neurotoxin injection to anal sphincter[101]
• Transit[102]
• Fibre
• Laxatives (osmotic, stimulant)
• Prokinetic drugs
• Secretagogues

Conclusions

- GI pathology in PD is various and common in PD.
- GI symptoms have a major effect on the well-being of PD patients.
- Integrative teams of devoted GI specialists and neurologist should evaluate and treat these cases.

Thank You

For Your Attention

Any Questions?