

Amyloidosis & the Gut

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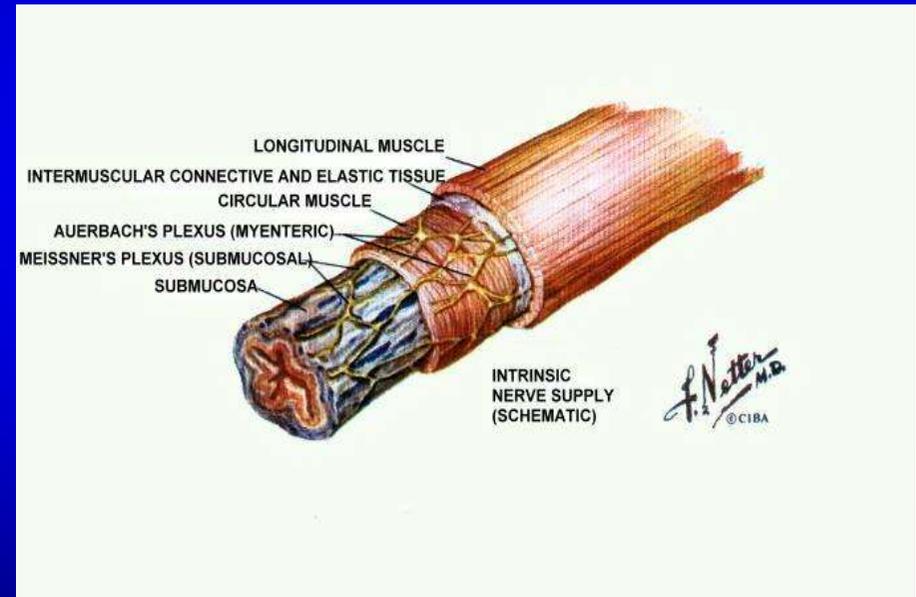
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Topics to cover

- 1) Patterns of GI amyloid involvement
- 2) Symptoms associated with amyloidosis
- 3) Diagnostic tests at our disposal
- 4) Treatment options
- 5) Epidemiology & data regarding variants

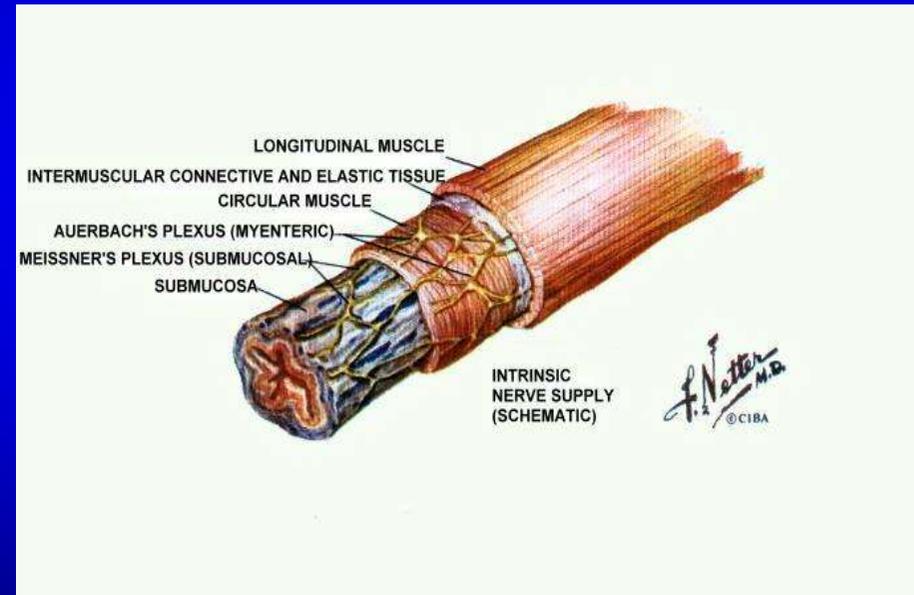
Patterns of GI amyloid

- Amyloid can deposit anywhere in the GI tract or nerves that regulate it
- Luminal GI Patterns:
 - Mucosal infiltration
 - Muscle infiltration
 - Neuropathy
 - Vascular



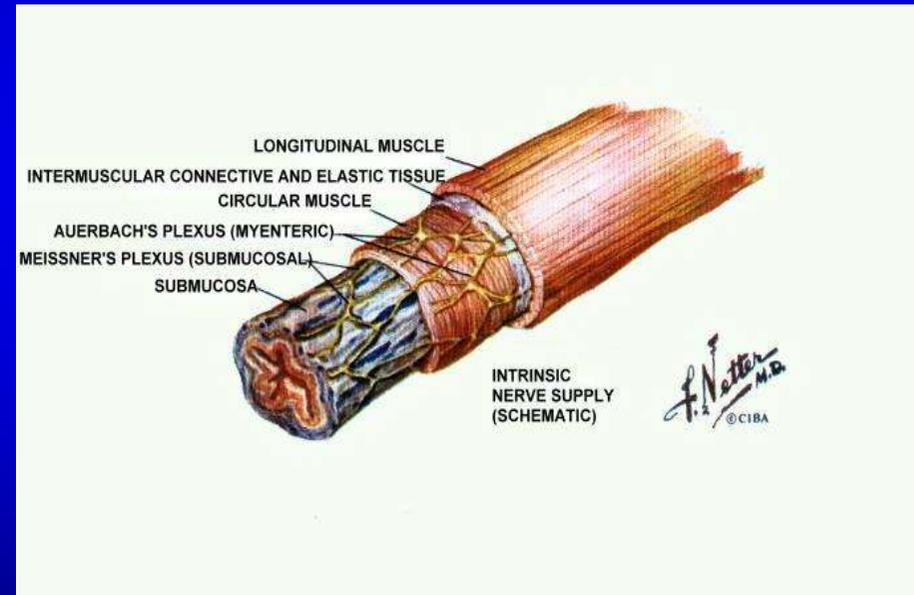
Patterns of GI amyloid

- Mucosal involvement
 - Role: site of absorption
 - Symptoms
 - Diarrhea
 - Malabsorption
 - Diagnosis
 - Endoscopic biopsy



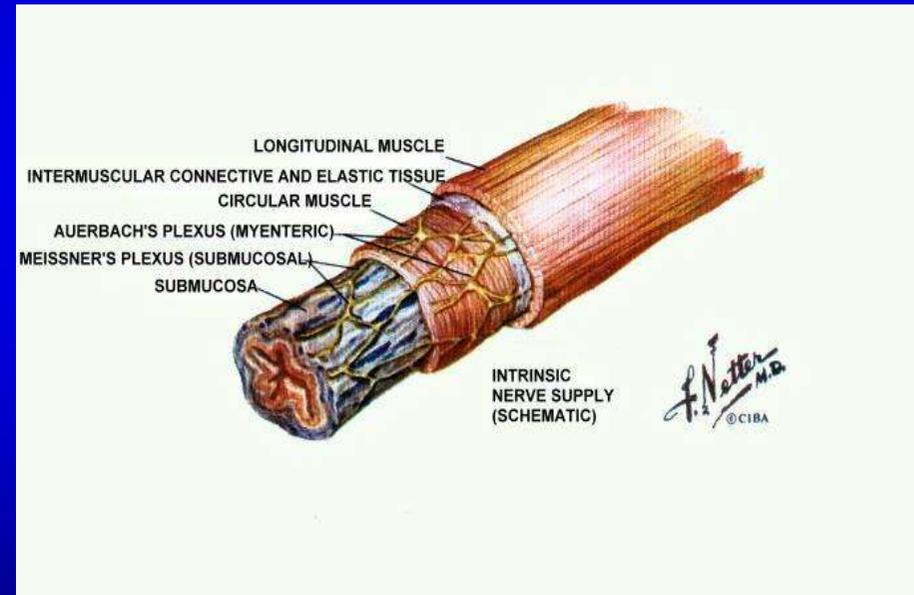
Patterns of GI amyloid

- Muscular infiltration
 - Role: site of contraction & motility
 - Symptoms
 - Decreased motility/stasis
 - Small intestinal bacterial overgrowth
 - » Diarrhea
 - » Malabsorption
 - Constipation
 - Pseudo-obstruction
 - Nausea/vomiting/abdominal pain
 - Diagnosis
 - Imaging studies
 - Transit studies
 - Manometry



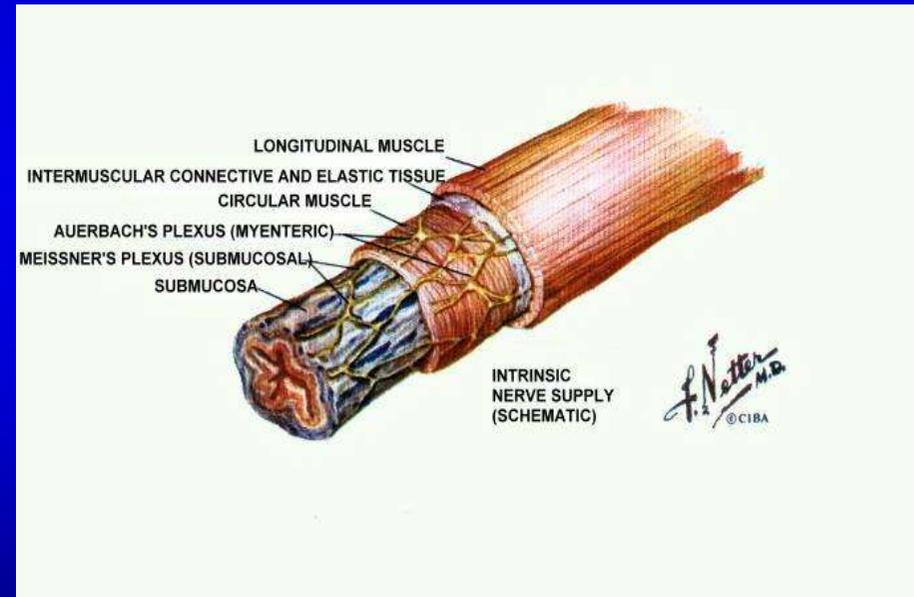
Patterns of GI amyloid

- Neuropathy
 - Role: coordination of GI motility & neuroendocrine secretion
 - Symptoms
 - Dysmotility
 - Nausea/vomiting/pain
 - Diarrhea
 - Constipation
 - Increased sensation
 - Diagnosis
 - Manometry
 - Transit studies



Patterns of GI amyloid

- Vascular
 - Role: delivery of blood flow to gut
 - Symptoms
 - GI Bleeding
 - Ischemia (pain/diarrhea)
 - Diagnosis
 - Endoscopy



Non-luminal GI patterns

- Liver involvement
 - Liver enlargement
 - Elevated liver tests (alkaline phosphatase)
 - Clinical manifestations usually mild but a marker of widespread systemic deposition
- Cholangitis
- Pancreas
- Peritonitis

Symptoms

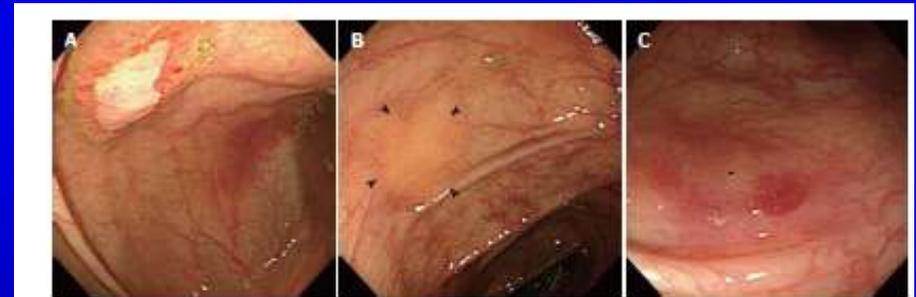
- Symptoms are linked to area of involvement & are often non-specific
 - Esophagus:
 - Reflux
 - Dysphagia
 - Food impaction
 - Stomach
 - Abdominal pain
 - Nausea
 - Vomiting
 - Distention
- Small intestine
 - Diarrhea
 - Malabsorption
 - Weight loss
 - Pseudo-obstruction
- Colon
 - Diarrhea
 - Constipation
 - Fecal incontinence

Symptoms Caveat

- When evaluating symptoms in amyloid, it is important to remember that most symptoms are nonspecific and can also be seen outside of amyloid
 - Reflux: 20% adults
 - Dysphagia: 4% adults
 - Functional dyspepsia: 20-30% adults
 - IBS: 13% adults
 - Constipation: 15% adults
 - Fecal incontinence: 6% adults
- Just because someone has amyloid, doesn't mean they can't have other GI conditions
 - Inflammatory bowel disease
 - Celiac disease
 - Eosinophilic esophagitis
 - Cancers
- Symptoms can also relate to medication adverse effects
 - GI symptoms most common adverse effects listed for most medications
 - > 80% of people who take 5 or more medications will have at least one adverse effect

Diagnostic tests

- Endoscopy & colonoscopy are usually the first tests performed
 - Allows option to take biopsies for diagnosis
 - Can also allow treatment
 - Bleeding control
 - Dilation
 - Findings can be nonspecific
 - Will only pick up mucosal GI involvement
 - Rectum commonly chosen as yield high (> 75%) and easy to get to
 - Highest yield in GI tract is in duodenum



Diagnostic tests

- Other tests to consider
 - Imaging studies
 - CT
 - MRI
 - Barium
 - Motility studies
 - Scintigraphy
 - Manometry
 - Wireless motility capsule
 - Sitz marker study
 - Breath tests



Treatment options

- Treatment should be tailored to symptoms & GI involvement

Treatment options

- Esophagus
 - Reflux treatment options
 - Dietary modification
 - Antacids
 - Histamine receptor blockers
 - Proton pump inhibitors
 - Endoscopic/surgical options in carefully selected patients
 - Dysphagia treatment options
 - Dietary modification
 - Dilatation
 - Botox

Treatment options

- Stomach
 - Dietary modification
 - Prokinetics
 - Metoclopramide (Reglan)
 - Erythromycin/azithromycin
 - Domperidone (not FDA-approved)
 - Prucalopride
 - Bethanechol
 - Pyridostigmine
 - Agents to help stomach expansion
 - Herbal therapies (peppermint/caraway)
 - Buspirone
 - Neuromodulators
 - Tricyclics (amitriptyline)
 - Mirtazapine (Remeron)
 - Gabapentin (Neurontin)
 - Gabapentin/pregabalin (Lyrica)
 - Anti-emetics
 - Endoscopic options: Botox

Treatment options

- Small bowel
 - Dietary modifications
 - Prokinetics
 - Antibiotics (focused on small intestinal bacterial overgrowth)
 - Octreotide
 - Steroids
 - Bile-salt binding agents
 - Anti-diarrheals
 - Imodium
 - Lomotil
 - Tincture of opium
 - Parenteral nutrition (rare cases)

Treatment options

- Colon
 - Dietary modifications
 - Laxatives
 - Over the counter
 - Miralax
 - Senna
 - Magnesium-based preparations
 - Prescription
 - Lubiprostone (Amitiza)
 - Linaclotide (Linzess)
 - Plecanatide (Trulance)
 - Prucalopride (Motegrity)*
 - Prokinetics

Epidemiology

- GI involvement in amyloid as a whole is (to me at least) reported to be surprisingly low:
 - 2013: In retrospective study of 2334 patients with amyloidosis, only 76 (3%) had amyloid on GI biopsies
 - 2015: In Korean study, only 24 of 155 symptomatic; all with amyloid on biopsy (15%)
 - 2017: In retrospective study of 583 amyloid patients, only 96 reported GI symptoms; 82 underwent endoscopy with biopsies; only 45% had amyloid on biopsies (16% symptomatic; 6% amyloid on biopsies)

Cowan AJ. Haematologica 2013

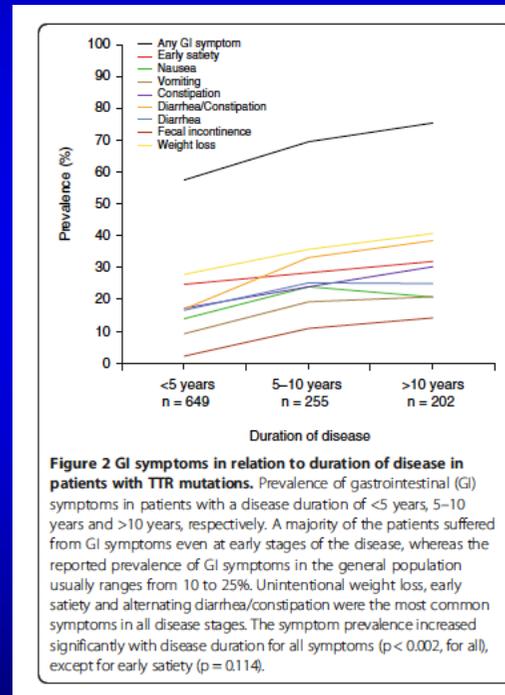
Young Lim A. Korean J Intern Med 2015

Yen T. Neurogastroenterol Motil 2017

Data regarding variants

- Extremely limited, but report from THAOS suggests GI manifestations are common
- Survey data from 1579 hereditary TTR amyloidosis (75% V30M) & 160 wild type analyzed
 - Hereditary: 63% GI symptoms
 - Wild type: 15% GI symptoms
- Most common symptoms:
 - Unintentional weight loss
 - Early satiety
 - Alternating diarrhea/constipation
- GI symptoms:
 - More common with V30M mutation versus other mutations
 - More common in younger onset patients (< 50)
- For patients with predominantly cardiac complications & wild type, the authors estimated that “the prevalence of gastrointestinal manifestations was not evidently higher than that expected in the general population”

Data regarding variants



Data regarding variants

Table 1 Most abundant TTR mutations and their clinical manifestations

| Mutation | Sensory neuropathy | Motor neuropathy | Gastrointestinal symptoms | Cardiac complications |
|----------|--------------------|------------------|---------------------------|-----------------------|
| V30M | 707 (89.5%) | 305 (38.6%) | 547 (69.3%) | 212 (26.9%) |
| V122I | 35 (60.3%) | 11 (19.0%) | 16 (27.1%) | 57 (96.6%) |
| S50R | 26 (89.7%) | 16 (55.2%) | 19 (65.5%) | 13 (44.8%) |
| E89Q | 21 (95.5%) | 10 (45.5%) | 13 (68.4%) | 13 (65.0%) |
| T60A | 16 (80.0%) | 5 (25.0%) | 8 (40.0%) | 19 (90.5%) |
| F64L | 18 (90.0%) | 11 (55.0%) | 10 (50.0%) | 7 (35.0%) |
| S77Y | 16 (94.1%) | 8 (47.1%) | 12 (70.6%) | 9 (52.9%) |
| I68L | 7 (46.7%) | 6 (40.0%) | 2 (13.3%) | 13 (86.7%) |
| I107V | 10 (83.3%) | 9 (75.0%) | 7 (58.3%) | 8 (66.7%) |
| G47A | 8 (72.7%) | 2 (18.2%) | 2 (18.2%) | 1 (9.1%) |
| L111M | 1 (10.0%) | 0 (0.0%) | 1 (10.0%) | 7 (70.0%) |

Mutations carried by ten individuals or more listed in a descending order.

Table 2 Distribution of GI symptoms in patients with ATTR amyloidosis

| Symptom | Wild-type n = 140 | TTR mutation n = 1114 |
|---------------------------|----------------------|--------------------------|
| Any GI symptom | 21 (15.3%) | 696 (63.0%) |
| Early satiety | 5 (3.6%) | 291 (26.4%) |
| Nausea | 3 (2.2%) | 189 (17.1%) |
| Vomiting | 0 (0.0%) | 147 (13.4%) |
| Constipation | 5 (3.6%) | 230 (20.9%) |
| Diarrhea/constipation | 2 (1.5%) | 267 (24.3%) |
| Diarrhea | 5 (3.6%) | 218 (19.8%) |
| Fecal incontinence | 0 (0.0%) | 68 (6.2%) |
| Unintentional weight loss | 4 (2.9%) | 346 (31.5%) |

Number of patients, n (%), reporting gastrointestinal (GI) symptoms at enrollment.

Conclusions

- Amyloid can cause symptoms by either direct deposition or nerve involvement
- Only the mucosa can be evaluated by endoscopy so the absence of amyloid on endoscopic biopsy does not exclude amyloid involvement
- Involvement appears to be common (60%) in familial amyloidosis, particularly in neuropathic variants
- Diagnostic options & treatment options exist and can be customized to specific symptoms

Thank you



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