Approach to the Patient: Infectious, Inflammatory, Neoplastic or Functional GI

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Infectious, Inflammatory, Neoplastic or Functional GI

- Approach to the patient with diarrhea
- Celiac Disease
  - Post-infectious
  - Inflammatory
  - Associated with Neoplasia
  - Masquerade as functional disease

Case 1

- 43yo female c/o diarrhea x 2 months
- Started while on trip to Mexico, where she had “food poisoning”
- Improved, but not resolved; now with 2-3 BM/d of loose stools and occ crampy abd pain that is relieved with BM
- no n/v / hematemesis/ wt loss/ BRBPR/ melena

Differential Diagnosis:
- Persistent Infection
- Post-infectious lactose intolerance
- Post-infectious IBS
- Unmasking of other GI disease: celiac, microscopic colitis
**Acute vs. Chronic Diarrhea**

- **Acute:** < 2 weeks
- **Persistent:** 2-4 weeks
- **Chronic:** > 4 weeks

**Acute Diarrhea: Patient Evaluation**

- Subset of patients with more severe disease:
  - Profuse watery diarrhea with dehydration
  - Dysentery, small volume stools with blood and mucus
  - Fever
  - Passage of >6 unformed stools / 24h or duration of illness >48h
  - Diarrhea with severe abd pain in patient above 50yo
  - Diarrhea in elderly (>70yo) or immunocompromised

**Acute Diarrhea: Patient Evaluation**

- Low rate of positive stool cultures
  - 1.5 – 5.6%
  - Self-limited
  - Giardia: at least half of patients with Giardiasis will have negative O&P – consider stool Giardia Ag
  - Severe diarrhea, moderate to high fever, fecal leukocytes or heme + stools are predictive of finding an identifiable pathogen
  - Role of endoscopy: Cdiff, immunocompromised, patients with h/o IBD, concern for sequelae of infection (i.e. dehydration leading to ischemic colitis)

**Acute Diarrhea: Therapy**

- Fluid and electrolyte therapy
- Symptomatic therapy:
  - Loperamide
  - Bismuth: if n/v prominent feature, or if fever/dysentery
- Empiric antibiotics
  - Modest reduction in time to cure: moderate to severe disease
  - Fluoroquinolones, Flagyl if Cdiff or Giardia suspected
  - Avoid in suspected/confirmed EHEC HUS
    - up to 10% of patients with EHEC infection may develop HUS, with a case-fatality rate ranging from 3% to 5% (WHO)
    - bloody diarrhea, abdominal pain and tenderness, but little or no fever

Guerrant et al, Clin Infect Dis 2001 Feb 1;32(3):331-51
AJG Guidelines for Acute Infectious Diarrhea in Adults 1997
Guerrant et al, Clin Infect Dis 2001 Feb 1;32(3):331-51
Persistent/Chronic Diarrhea: Infectious etiologies

- C difficile
- Bacterial: Aeromonas, Plesiomonas, Campylobacter
- Parasitic: Giardia, Amebae, Cryptosporidium, Cyclospora

Post-Infectious IBS

- In the year after an episode of gastroenteritis, patients are 6-10 times more likely to have IBS than subjects in the general population.
- Low-grade inflammation involved in sx generation?
- Predictive factors:
  - Female gender, use of antibiotics
  - Vomiting during the acute illness
  - Young age, prolonged fever, anxiety and depression

Case 1

- Stool studies:
  - Bacterial: Aeromonas and Pleisomonas
  - O&P
  - Cdff
- Given duration, important to consider other causes of chronic diarrhea

Approach to the Patient: Chronic Diarrhea

- Inflammatory
- Watery
- Fatty

References:
Approach to the Patient: Chronic Diarrhea

- Inflammatory
  - Infectious
  - Idiopathic inflammatory bowel disease
- Watery
  - Osmotic
  - Secretory
- Fatty
  - Maldigestion
  - Malabsorption

Onset and duration of symptoms
Travel, sick contacts
Character of stool: #BM/d, volume, fatty or watery stools
Relationship to food
Nocturnal symptoms
Blood in BMs
Tenesmus
Weight loss

Inflammatory Diarrhea

- Differential:
  - IBD: ulcerative colitis, chron’s disease
  - Infectious
  - Ischemic
  - Radiation colitis
  - Neoplasia
  - Hx: tenesmus, bloody diarrhea, nocturnal BMs, wt loss, family h/o IBD
- w/u:
  - labs (CBC, ESR, CRP; LFTs with albumin)
  - Stool studies:
    - Fecal leukocyte: Sn 70% and Sp 50% for detecting inflammation in infectious diarrhea
    - Heme-occult
    - Colonoscopy

Watery Diarrhea

- Differential of Osmotic Diarrhea:
  - Ingestion of exogenous magnesium
  - Carbohydrate malabsorption
  - Consumption of poorly absorbable carbohydrates
  - Stool pH < 6
- Hx: diarrhea is worse after eating; h/o eating sugar-free gums or candies
**Watery Diarrhea**

- Differential of Secretory diarrhea:
  - Infectious: small and large bowel pathogens
    - Aeromonas, Plesiomonas, Giardia, Cryptosporidium
  - Bile acid malabsorption
  - Microscopic colitis
  - Endocrine: DM, hyperthyroidism, Addison’s
  - Peptide-secreting endocrine tumors
- Hx: continues despite fasting
  - Stool volumes > 1L/day

**Watery Diarrhea: work-up**

- Labs: CBC, electrolytes
- Stool Osmolality
  - Osmotic gap: $290 - 2(NA + K)$
  - > 125: osmotic diarrhea
  - < 50: secretory diarrhea
- Osmotic:
  - Stool ph < 6
  - Trial of lactose-free diet
  - Breath test
- Secretory:
  - Trial of bile acid binders
  - Stool cultures
  - Imaging of small and large bowel
  - Testing for secretagogues

**Fatty Diarrhea**

- Maldigestion
  - Pancreatic exocrine insufficiency: alcoholic pancreatitis, senile atrophic pancreatitis
  - Inadequate luminal bile acids
- Malabsorption
  - Mucosal disease: celiac sprue
- Elderly: celiac sprue, pancreatic insufficiency, bacterial overgrowth

**Fatty Diarrhea**

- History: weight loss, fatty or oily stools, difficult to flush
- w/u:
  - Labs: CBC, albumin
  - Stool for fecal fat
    - Qualitative: Sudan stain, can predict 90% of patients with clinically significant steatorrhea.
    - Quantitative: 72-hour stool collection, on high fat diet
  - Imaging: $\pm$ chronic pancreatitis
  - Endoscopy with small bowel biopsy: $\pm$ sprue
  - Breath test for bacterial overgrowth

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My general approach to diarrhea

- History
- Labs:
  - CBC with diff
  - ESR/CRP
  - Lytes
  - LFTs with albumin
  - TTG
  - Stool: r/o infection (bacteria, O&P, Cdiff); fecal fat
- EGD with SB biopsy / colonoscopy or flex sig with biopsy
- Imaging, breath tests

Systematic evaluation of causes of chronic watery diarrhea with functional characteristics

- 62 pts
- >3 BM/d of loose or liquid stools
- Diagnosis:
  - Bile acid malabsorption 45.2%
  - Sugar malabsorption 16.1%
  - Celiac disease 16.1%
  - 19.4% no diagnosis
- Conclusion: the diagnosis of functional disease in patients with chronic watery diarrhea should be performed with caution since in most cases there is an organic cause that justifies diarrhea

Case 2

- 28 yo female
- 6 year h/o “IBS”: abd gas, bloating, diarrhea alternating with constipation
- Tried on multiple medications without relief
- Friend told her she might have Celiac Disease

Case 2

“Doc – what is celiac disease?“
“What is celiac disease?”

- Permanent intolerance to gluten
- Dietary gluten can cause complex adaptive and innate immune reactions resulting in chronic inflammation of the mucosa

Pathogenesis of Celiac Disease: Gluten

- Wheat
- Rye
- Barley

Pathogenesis of Celiac Disease: HLA-DQ2/HLA-DQ8

Case 2

“How common is it... why haven't I heard about this before?”

US: 1:100 (range 1:80 to 1:140)

Estimated that less than 5% of those with CD in the US are currently diagnosed

For every 1 CD diagnosis, 3-7 undiagnosed CD cases

“Classic symptoms”

Clinical Presentation

- Classic
- Atypical
- Silent
- Latent
- Refractory
Clinical Presentation

- **Classic**: Intestinal malabsorption
- **Atypical**
- **Silent**
- **Latent**
- **Refractory**

**Classic**
- Atypical: Most common; little or no GI symptoms. Ex: fe def, osteoporosis
- **Silent**
- **Latent**
- **Refractory**

**Silent**
- Asymptomatic patients with gluten-induced villous atrophy
- **Latent**: Previous dx that responded to GFD who retain normal mucosal histology or have only an increase in IEL; or, currently normal histology on gluten-containing diet who will subsequently develop CD
- **Refractory**

Clinical Presentation

- Classic
- Atypical
- Silent
- Latent
- Refractory: true CD, do not respond to GFD

Detection of CD in Primary Care

- Survey of adult celiac patients in NY
  - Mean diagnostic delay 5.8 (0.5) yrs
- Survey of adult celiac patients in USA
  - Majority dx in 4th – 6th decade
  - Symptoms present a mean of 11 yrs before dx
  - 77% reported improved quality of life after dx, even if dx > 60yo
- Survey of PMDs in southern CA
  - Medical practice for average of 20 yrs
  - Only 35% had ever diagnosed a pt with CD

Detection of CD in Primary Care: A multicenter case-finding study in North America

- Multicenter, prospective study 2002-2004
- Any individual over 18yo with 1+ symptom:
  - Family h/o Celiac Disease
  - Unexplained anemia or f bleeding
  - Recurrent abd pain or bloating
  - IBS or chronic diarrhea (longer than 2 weeks)
  - Chronic fatigue
  - Abnl LFTs
  - Autoimmune disorders (Type I DM, thyroiditis, autoimmune hepatitis, RA, connective tissue d/o, vitiligo, Sjogren’s)
  - Down’s
  - Turner’s
  - Infertility
  - Epilepsy or ataxia
Detection of CD in Primary Care: A multicenter case-finding study in North America

- 737 women, 239 men
- Median age 54.3 yrs
- Positive anti-tTG 3.07% (30); CD in 2.25% (22)
  - Most frequent reason: bloating (12), thyroid disease (11), IBS (7), unexplained chronic diarrhea (6), chronic fatigue (5), constipation (4)
- Dx rate increased from 0.27 cases per thousand visits at baseline to 11.6 per thousand visits following active screening implementation
  - 32-43 fold increase in diagnosis of CD

NICE Guidelines

- In patients suspected of having IBS, to exclude other diagnoses recommend
  - CBC
  - ESR/CRP
  - Antibody testing for celiac disease

Celiac Disease: a systemic disease

- Relatives: 10%
- Fe def anemia
  - Asymptomatic: 5% serology, 8.7% biopsy
  - Symptomatic: 10.3-15%
  - Should be considered in any adult with unexplained IDA, including menstruating women
- Liver Disease:
  - 1.5-9% LFT abnormalities of unknown cause
- Osteopenia/Osteoporosis
  - 1% and 3.4%
  - Should be considered in any patient with premature onset osteoporosis
- Infertility
  - The pooled relative risk of celiac disease in infertile women compared with controls was 3.7 (95% CI, 1.3–10.4).
QOL in Patients with Screen-Detected Disease

- Prospective study of patients before and 1 yr after initiating a GFD in Finland
  - 19 pts with screen detected disease (first degree relatives of celiac patients)
  - 21 consecutive patients with symptom-detected CD
- Gastrointestinal Symptoms Rating Scale (GSRS)
- QOL measured by Psychological General Well-Being Questionnaire (PGWB)
- Main finding: with GFD, most patients with symptom-detected disease and most of the patients with screen-detected disease reported improved GSRS and PGWB scores

Case 2

- “How do we diagnose it?”

Serology

- IgA tTG
  - Specificity > 95%
  - Sensitivity 90-96%
- IgA EMA: more time consuming, operator dependent
  - Specificity 99.6%
- Routine measurement of IgA not warranted unless IgA deficiency strongly suspected

Duodenal Biopsy

- Duodenal biopsy: Gold Standard
  - Sensitivity of serologic tests in certain clinical circumstances and the potentially low PPV of serologic tests in usual clinical practice has been questioned
- Ideally 6 biopsies: mucosal changes can be patchy
- Second duodenum or beyond
**Endoscopy for Diagnosis:**

- **Endoscopic signs:**
  - Decrease in duodenal folds
  - Scalloping of folds
  - Mucosal fissures
  - Nodularity

**Pathological Diagnosis**

- Villous atrophy
- Crypt hyperplasia
- Increased intraepithelial lymphocytes: >30-40 per 100 surface enterocytes

**Case 2**

- “Oh, I already feel so much better after starting on the diet…”

**Common Pitfalls in Diagnosis of CD**

- Gluten reduced diet may reduce severity of lesion and impact pathological interpretation
- 4-week challenge with sufficient gluten
**Case 2**

- “No way am I going back on a gluten diet…”

**HLA-DQ2 and DQ8**

- 95% CD patients have DQ2
  - DQA1*05 and DQB1*02
- 5% DQ8
  - DQA1*03 and DQB1*0302
- Absence of these alleles provides a NPV close to 100%

**Algorithm: suspected CD**

**GFD**

Table 2: Fundamentals of the Gluten-free Diet.

- **Grains that should be avoided**
  - Wheat (includes spelt, kamut, semolina, triticale), rye, barley (including malt)
- **Safe grains (gluten-free)**
  - Rice, amaranth, buckwheat, corn, millet, quinoa, sorghum, teff (an Ethiopian cereal grain), oats
- **Sources of gluten-free starches that can be used as flour alternatives**
  - Cereal grains: amaranth, buckwheat, corn (polenta), millet, quinoa, sorghum, teff, rice (white, brown, wild, basmati, jasmine), maize (Indian rice grass)
  - Tapioca: arrowroot, jicama, taro, potato, tapioca (cassava, manioc, yucca)
  - Legumes: chickpeas, lentils, kidney beans, navy beans, pea beans, peanuts, soybeans
  - Nuts: almonds, walnuts, cashews, hazelnuts, macadamias
  - Seeds: sunflower, flax, pumpkin
Case 2

- “If I do have celiac disease, am I going to die from it?

Mortality and CD

- SMR: 1.9 – 3.4
- Risk of death higher among patients
  - presenting with malabsorption (SMR 2.5)
  - Not adhering to GFD (SMR 10.7)
  - Diagnostic delay
- No excess mortality seen in patients with mild or asymptomatic disease

Case 2

- “Will I get cancer?”

Malignancy and CD

- Increased risk of lymphoma: SIR 2.7-6.3
- Other cancers:
  - Esophageal, stomach, pancreas, liver, biliary, small bowel, pleura, melanoma and leukemia
- Adherence with GFD likely protective against NHL
Patients with celiac disease should be evaluated at regular intervals by a healthcare team including a physician and a dietician. These visits can be used to assess, by history, a patient’s compliance with a GFD and to reinforce the importance of such compliance. Beyond this, there are no clear guidelines as to the optimal means to monitor adherence to a GFD. Repeat serologic testing after 6 months or more on a GFD. The serologic test results tend to become negative as the histologic findings improve. tTGA or EMA can distinguish between compliers and noncompliers. Sensitivity for minor dietary indiscretion can be LOW.

- Common disorder with variable manifestations
- Inflammatory disorder of the intestines that can lead to malabsorption and malnutrition
- Can be unmasked – “post-infectious”
- Can masquerade as functional disease
- Potential neoplastic consequences