Implications of Gluten Intolerance and Celiac Disease in IBS

Joseph A. Murray, MD, FACG
Mayo Clinic, Rochester, MN

Outline

- Similarity to IBS symptoms
- Celiac disease is well defined disease
- Non-Celiac Gluten sensitivity is not so well defined nor certain as an entity
What is Celiac Disease?

- It is an inflammatory state of the small intestine that occurs in genetically predisposed individuals and resolves with exclusion of dietary gluten.

Who Gets Celiac Disease?

- Adults >> children, female > males
- Worldwide, mostly Caucasians
- Any age including elderly
- People with other immune disorders
  - Type one diabetes mellitus
  - Sjogren’s syndrome
  - Thyroid disease
  - Lupus, Addison’s disease
- Family members of celiacs
World Map Indicating Prevalence of Celiac Disease


Presentations of Celiac Disease

- Classic malabsorptive syndrome (25%)
  - diarrhea, steatorrhea, weight loss, multiple deficiencies
- Monosymptomatic (50%)
  - Anemia, diarrhea, lactose intolerance, constipation
- Acute Abdomen (rare)
  - abdominal pain, intussception, vomiting, obstruction, perforation, lymphoma
- Non-GI presentations (25%)
  - Infertility, bone disease, neurological disease, short stature, brittle diabetes, chronic fatigue, abnormal LFTS
**Clinical Spectrum of Celiac Disease and IBS**

**IBS-like symptoms**

**Spectrum of CD**

- Potential CD
- Latent CD
- CD and complications

Murray et al, AJCN 2004
Adapted from Verdu et al, 2009

---

**Celiac Disease in IBS**

- Increased in secondary referrals for IBS
- No increase in community study
- No increase in multicenter study
- Celiac disease not predicted by IBS symptoms in population based studies

---

1 Sanders et al. Lancet 2001
2 Locke et al. MCP 2005
3 Cash et al. Gastro 2011
4 Katz et al AJG 2012
5 Walker et al. Gastro 2012

Bottom line: if someone has sent you a presumed IBS patient not tested for CD: test them!
Prior IBS Diagnoses in Celiac Disease

- Current literature suggests a preceding IBS diagnosis is frequently made in celiac patients (18.1 - 36 %)
- Data predominantly from patient reported surveys, estimating 29-36% (4-6)

Delay to Celiac Diagnosis?

- Celiac disease is not being promptly diagnosed
  - Symptom durations ranging from 7 to 12.9 years,
- A prior diagnosis with IBS may result in further delays in celiac diagnosis by as much as 3-4.9 years

Green et al. AJG 2001
Cranney et al. DDS, 2007
Baratt et al. DDS 2008
Corazza et al. 1996
Detection versus Diagnosis

- Detecting CD is the not the same as confirming it!
- For detection you do not want to miss a case; maximize sensitivity
- For diagnosis you need confirmation: maximize specificity
- Serology first then biopsy confirmation

* ACG Guidelines on celiac disease

Comparison of Serological Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
<th>Tech</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>HtTg</td>
<td>96-98</td>
<td>88-100</td>
<td>Low</td>
<td>$$</td>
</tr>
<tr>
<td>EMA</td>
<td>75-98</td>
<td>99-100</td>
<td>High</td>
<td>$$$$</td>
</tr>
<tr>
<td>Gliadin-IgA</td>
<td>53-100</td>
<td>65-100</td>
<td>Low</td>
<td>$</td>
</tr>
<tr>
<td>Gliadin-IgG</td>
<td>57-100</td>
<td>42-98</td>
<td>Low</td>
<td>$</td>
</tr>
</tbody>
</table>
## Comparison of Serological Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
<th>Tech</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>HttG</td>
<td>96-98</td>
<td>88-100</td>
<td>Low</td>
<td>$$</td>
</tr>
<tr>
<td>EMA</td>
<td>75-98</td>
<td>99-100</td>
<td>High</td>
<td>$$ $$ $$</td>
</tr>
<tr>
<td>Gliadin-IgA</td>
<td>53-100</td>
<td>65-100</td>
<td>Low</td>
<td>$</td>
</tr>
<tr>
<td>Gliadin-IgG</td>
<td>57-100</td>
<td>42-98</td>
<td>Low</td>
<td>$</td>
</tr>
<tr>
<td>Deamidated Gliadin P</td>
<td>80</td>
<td>95</td>
<td>Low</td>
<td>$</td>
</tr>
</tbody>
</table>

Sensitivity of TTg-IGA

- Schwertz: 0.94 (0.84 – 0.99)
- Sugai: 0.97 (0.91 – 0.99)
- Agardh: 0.97 (0.92 – 0.99)
- Kaukinen: 0.89 (0.75 – 0.96)
- Ankelo: 0.90 (0.81 – 0.95)
- Niveloni: 0.95 (0.86 – 0.99)
- Volta: 0.97 (0.92 – 0.99)
- Szabo: 1.00 (0.95 – 1.00)
- Naiyer: 0.89 (0.72 – 0.98)
- Naiyer: 0.93 (0.76 – 0.99)
- Rashtak: 0.78 (0.68 – 0.86)
- Basso: 0.93 (0.87 – 0.96)

Pooled sensitivity = 0.93 (0.91 to 0.94)
Chi-square = 43.80; df = 11 (P = 0.0000)
Inconsistency (I-square) = 74.9 %

Lewis and Scott; APT, 2010, vol:31, iss:31, pg 73-81
Decrease in Sensitivity of ELISA Tests After Treatment with GFD

Also beware of IgA deficiency

Challenging the Supremacy of Biopsy
New ESPGHAN Guidelines for Kids

- Biopsy can be avoided if all of the following apply:
  - tTg-IgA > 10 x upper limit of normal
  - Symptoms suggestive of celiac disease
  - EMA+
  - HLA = DQ2 or DQ8
  - Responds to gluten diet

Husby et al, JPGN 2012
How Good is Serology in Practice

- Specificity of the tests
  - TTg-IGA high >95%
  - EMA-IGA high 76*-100%
- Variability:
  - Lab to lab
  - Kit to kit
  - Reference ranges
  - Performance
- Biopsy still endorsed by ACG as central to diagnosis

* Mubarak et al, JPGN 2011

Need to biopsy duodenal bulb in seropositive patients

Pancreas

Papilla of Vater

Duodenum

1-2

4+
Gluten Sensitive Enteropathy

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>IIIa</th>
<th>IIIb</th>
<th>IIIc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Few or no symptoms</td>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Little malabsorption</td>
<td>Minimal malabsorption</td>
<td>Extensive malabsorption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No villous atrophy</td>
<td>Partial villous atrophy</td>
<td>Complete villous atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Little crypt hyperplasia</td>
<td>Some crypt hyperplasia</td>
<td>Marked crypt hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased IELs</td>
<td>Increased IELs</td>
<td>Increased IELs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What About Patients on GFD Diet?

- Often unhappy patient if symptomatic
- Serology and biopsies can normalize
- HLA type might help
- Challenge
- Some patients will not eat gluten
- Why argue with success if diet is nutritionally adequate?
**Celiac Disease and HLA Risk**

- **Celiac disease**
  - General population
  - HLA DQB1*02/DQA*05(DQ2)
  - or DQB1*0302/DQA1*03 (DQ8)

**When to Use HLA?**

- People on a gluten free diet (including refractory)
- Seronegative positive biopsy patients
- Those at genetic risk who are seronegative
  - Down's Syndrome
  - Turner's syndrome
  - William's syndrome
  - Asymptomatic family members
  - Type one diabetes

Usual prevalence of DQ2

High prevalence of DQ2/8
Prevalence of Celiac Disease and Gluten Free Diet: NHANES 2009-2010

Gluten Free Diet

- GFD without Dx of CD
- 1.6 million

Celiac Disease

- Diagnosed CD
- 17%
- Untreated CD
- 83%
- 1.8 million
- 1% of Caucasians

Rubio-Tapia, et al. AJG 2012

Why the worry about gluten?

Clinical Spectrum

Gluten sensitivity (GS)

IBS-like symptoms

Potential CD
Latent CD
CD and complications

IBS
Lactose intolerance
Food intolerance
SIBO

Spectrum of CD

Adapted from Verdu et al. 2009

Non Celiac Gluten Sensitivity as a Clinical Entity

- Gluten-sensitive diarrhea without celiac disease first described as a clinical entity in 1980
- Females, chronic diarrhea, increased cellular infiltration of lamina propria
- 3-month gluten-free diet (GFD)
- HLA DQ2 associated with celiac disease
- Chronic Diarrhea patients with HLA-DQ2 expression profit from a gluten-free diet

(Wahnschaffe, Gastroenterology, 2001)
HLA-DQ2 positive IBS patients had markers (IELS or gliadin sIgA)

- Cohort of 102 IBS patients, 35% (n=36), were HLA DQ2+
- All were TTG IgA -
- 36% of HLA + IBS patients had ↑ IEL’s
- 58% had + IgA gliadin or TTG in aspirate.

Normalization of GI symptom score and stool frequency achieved with GFD

- N=41 IBS-D
- 6-month GFD
- GI symptoms and stool frequency
- HLA DQ2 status and IgG TTG/AGA may predict clinical response to a GFD
- Histology does not predict response
- TTG IgG, GS marker?
Non Celiac Gluten Sensitivity

Condition of morphological, immunological, or functional disorder that responds to gluten exclusion in the absence of celiac disease.

- Gluten sensitive diarrhea
- Immunopathological changes in the SB mucosa
  - ↑ Intraepithelial lymphocytes (IEL)
  - ↑ IgA deposits intestinal villi
  - ↑ Secreted Ab against gliadin
  - HLA predicted

Adapted from Verdu EF, et al. AJG, 2009.
Ludvigsson et al. Gut 2012

Gluten Sensitive GI Symptoms “Celiac Like”

- Self identified gluten sensitivity
- Gi Symptoms
- Challenge study
- Randomized
- Double blind placebo controlled
- Effect not HLA dependent
- Highly select group

“Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial”
Biesiekierski JR et al. AJG 2011
Follow Up Study

- Self declared gluten sensitive
- Repeat trial
- Run in with low FODMAPs
  - All symptoms disappeared
- Challenges induced symptoms
- Only 8% responded to Gluten
- Not reproduced on rechallenge
- Order effect: Nocebo

Biesiekierski JR et al. Gastro 2013

---

**Figure 1** Individual responses in mean overall symptom severity score during the run-in period, where low FODMAP diet was commenced, compared with the baseline period, where participant's usual gluten-free diet was consumed during 7-day trial. Scores were s...

Jessica R. Biesiekierski, Simone L. Peters, Evan D. Newnham, Ourania Rosella, Jane G. Muir, Peter R. Gibson

No Effects of Gluten in Patients With Self-Reported Non-Celiac Gluten Sensitivity After Dietary Reduction of Fermentable, Poorly Absorbed, Short-Chain Carbohydrates

Gastroenterology Volume 145, Issue 2 2013 320-328.e3

http://dx.doi.org/10.1053/j.gastro.2013.04.051
**Follow-up Study Design**

Enrolled: n = 250
- Did not return recruitment survey (101)
- Coeliac disease not excluded (92)
- Not gluten-free (42)
- Symptomatic on gluten-free diet (36)
- Unwillingness to participate - time (9); travel (20); did not want to eat gluten (8)

Screened: n = 149
- Due to one or more

7-day trail Randomized: n = 40
- Inadequate symptom control during run-in (3)
- Pregnant/breast-feeding (3)
- Travel (3)
- Time (6)
- Did not want to eat gluten (4)

Per-protocol Randomized: n = 37

3-day rechallenge Randomized: n = 22

---

**A Controlled Trial of Gluten-Free Diet in Patients With Irritable Bowel Syndrome-Diarrhea**

(A) Diet effect on stool frequency (*P = .04*), form, and ease of passage; the effect on stool frequency was greater in HLA-DQ2- or HLA-DQ8-positive patients (*P = .019*).

(B) Mean bowel movements per day during 14-day baseline and 28-day diet.

Vazquez-Roque et al. Gastroenterology Volume 144, Issue 5 2013 903-911.e3
A Controlled Trial of Gluten-Free Diet in Patients With Irritable Bowel Syndrome-Diarrhea

Gluten free diet reduced stool frequency
Benefit associated with HLA DQ2/8
Gluten free naïve IBS-D patients

Small Bowel Permeability Decreased on GFD
Gluten Sensitivity as a clinical entity: “Celiac-Lite”

- Genetic susceptibility: HLA DQ2/DQ8
- Loss of gluten tolerance

Celiac disease:
- Serum TTG Ab +
- Mucosal atrophy +

Gluten Sensitivity:
- ↑ IEL +
- Serum TTG Ab -
- No mucosal atrophy
- Response to GFD

Non Celiac Gluten Sensitivity = “Celiac Lite”

Condition of morphological, immunological, or functional disorder that responds to gluten exclusion in the absence of celiac disease.

- Gluten sensitive diarrhea
- Immunopathological changes in the SB mucosa
  - ↑ Intraepithelial lymphocytes (IEL)
  - ↑ IgA deposits intestinal villi
  - ↑ Secreted Ab against gliadin
  - HLA predicted

Adapted from Verdu EF, et al. AJG, 2009
Lymphocytic Duodenosis

- AKA Marsh 1
- >25 IELS/100 enterocytes
- Normal architecture
- 10-20% are part of the spectrum of gluten sensitivity
- Also NSAIDS, H pylori, Crohn’s, Sjogren’s syndrome

Kakar et al. AJG, 2003
VandeVoort et al. AJG 2009

Minimal histology +/- IBS-like symptoms

- TTG Ab positive
  - GFD

- TTG Ab negative
  - Genotyping
    - HLA DQ2/8 +
      - GFD
    - HLA DQ2/8 -
      - Other causes
  - Consider rebiopsy 3-6 months
  - GFD trial?

Adapted from Verdu EF, et al. AJG 2009
Are there other potential mechanisms of gluten in symptoms in IBS?

Multiple innate immune gluten-mediated effects

**Stress pathways**
- α gliadin p31-43
- LGQQQFPFPQQP
- Tryptic digested gliadin
- Epithelial activation
- Upregulation of IL-15 and EGFR
- Upregulation of stress-induced MHC-Ib

**Receptors pathways**
- Gluten
- FOQPQQQPQQPQQPQ
- SQQPQLLOQ
- Tryptic digested gliadin
- APC maturation
- Inflammatory cytokines
- IFN-α

**HLA-E surface expression and stabilization**
- APC activation
- Inflammatory cytokines
- IFN-α

**Increased intestinal permeability**
- APC
- TLR-4?
Evidence Lacking for Non Celiac Gluten Intolerance

- Prospective studies
- Clear syndrome definition lacking
- Association (eg Gliadin-Ab) does not equal cause
- Adequate and appropriate controls
  - Gluten sensitive IBS versus IBS
- Gluten dependence (DB RCT)*
  - De-challenge
  - Challenge
- Proven Gluten Exclusivity
  - Other parts of wheat (ATIs)
  - Other foods/dietary factors FODMAPS
  - Confounding problems “The Gut hurts!”

Summary

- Test for celiac disease before trying GF diet
- Do the right tests Serology + BX
- Ok to try GF in IBS patients but
- Beware nocebo effect
- Also stop GFD if benefit does not last
- Look elsewhere for explanations
- Is diet nutritionally adequate?
Is Gluten Evil or a Convenient Scapegoat?