Updates on Celiac Disease and Gluten Sensitivity

Sheila E. Crowe, MD, FRCPC, FACP, FACG, AGAF
Department of Medicine
University of California, San Diego

Case Presentation

• A 28 year old woman comes to see you for possible celiac disease. She reports abdominal bloating and discomfort, increased loose stools ranging from 2 to 3 a day without blood. She also complains of fatigue and headaches.

• On the advice of a friend she went on a gluten free diet two months ago. She feels better but wants to know if she has celiac disease and if she should stay on her diet which she finds expensive and difficult to adhere to. She also wonders about food allergies since even off gluten she gets symptoms with other foods.

How do you address the patient’s concerns?

Issues for Consideration

• What clinical presentations suggest celiac disease
• How to screen and diagnose celiac disease
• Role of genetic testing
• How to evaluate someone already on a GFD
• What about non-celiac gluten or wheat sensitivity
• Contribution of other food sensitivities
• Follow up of patients with celiac disease

What to Eat and What Not to Eat?

• Nearly every patient who sees a GI practitioner wants to know is it something they eat and/or is it something they are missing from their diet that is the cause of their GI and other health problems
• The popularity of many types of diets underscores the notion that what we eat is the key to health and wellbeing
• Marketing of food promoting potential health benefits is becoming more common

Definitions and Terminology

• Celiac disease (CD): a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals
• Other terms including celiac sprue, sprue, gluten intolerance and gluten-sensitive enteropathy are no longer recommended
• Classical and non-classical celiac disease
• Asymptomatic or subclinical celiac disease
• Potential celiac disease

Changing Prevalence of Celiac Disease

• Prevalence of up to ~1:100 in most genetically susceptible populations, 0.71% in NHANES study
• Less than 10-15% of current cases of CD have been diagnosed in the US
• CD is 4 to 4.5 times more prevalent than 50 yrs ago
• Cause of “CD epidemic” unknown
  – Dietary – grains with increased gluten, increased wheat in diets worldwide
  – Other environmental
  – Microbiota


Rubio-Tapia, Am J Gastroenterol, 2012
Rubio-Tapia et al, Gastroenterology, 137: 88, 2009
Virta et al, Scand J Gastroenterol, 44:933, 2009
Rubio-Tapia et al, Gastroenterology, 137: 157, 2009
Who Develops Celiac Disease?
Genetic and Other Factors

- Increased frequency of HLA haplotypes: DR3-DQ2, DR5/7-DQ2, DRA-DQB
- Other factors involved since most with these haplotypes do not get celiac disease (confer ~40% of risk)

Risk Factors: The Grains

- Environmental factors: Infectious agents
- Cytokines released during infection: Affecting APCs (e.g., dendritic cells)
- Cross-reactive amino acid sequences: Adenovirus, H. pylori

Varying Forms of Celiac Disease

- Classical celiac disease of childhood
- Late onset, non-specific GI symptoms
- Dermatitis herpetiformis
- Extra-intestinal presentations (many)
- Associated conditions (many)
- Silent or asymptomatic celiac disease (relatives)
- Latent or potential celiac disease

Celiac Disease: “Classical”

- Failure to thrive
- Weight loss
- Protuberant abdomen
- Bloating
- Diarrhea, steatorrhea
- Abdominal pain
- Dramatic response to gluten free diet

Changing Picture of Disease

- Classical form less prevalent now
- Average age of diagnosis in 5th decade
- Many are overweight
- Seroprevalence M=F, diagnosis M<F
- Other presentations are being increasingly recognized:
  - Obstetrical problems
  - Neuropsychiatric manifestations
  - Related autoimmune conditions
  - Many others – true associations or chance?

Symptoms and Conditions That Should Prompt Consideration of Celiac Disease

- GI symptoms
- Autoimmune endocrine disorders
- Autoimmune connective tissue disorders
- Hepatobiliary conditions
- Miscellaneous conditions
- Extraintestinal presentations
- Other inflammatory luminal GI disorders
- First and second degree relatives
Common Symptoms in Celiac Disease

- Altered bowel habits
  - Diarrhea, constipation and mixed pattern
- Fatigue
- Borborygmi, flatulence
- Abdominal discomfort or pain
- Weight loss
  - However patients with CD can be overweight and even obese
- Abdominal distention or bloating
- Note that there are many other presentations of celiac disease including an asymptomatic state


IBS or Celiac Disease?

- Some studies suggested a subset of patients diagnosed as IBS may have celiac disease
  - Wahnschaffe et al, Gastroenterology, 121:1329, 2001
  - Sanders et al, Lancet, 358:1504, 2001
- Decision analysis studies suggest that there is an acceptable cost of testing for celiac disease in IBS-D patients
  - Spiegel et al, Gastroenterology, 126:1721, 2004
  - Ladabaum et al, Aliment Pharmacol Ther 19:1199, 2004
- Over 4-fold increase prevalence of celiac disease in IBS cases compared to controls in a meta-analysis
- One USA study reports prevalence of CD in non-C IBS is similar to controls
  - ACG recommendations for evaluation of IBS-D include screening for celiac disease but not infection, IBD, CRC

Associated Hepatobiliary Conditions

- Primary sclerosing cholangitis
- Autoimmune cholangitis
- Primary biliary cirrhosis
- Elevated transaminases (up to 5X normal)
  - Nonspecific histologic changes
  - Normalize on GFD within a year in 75-95%
  - Evaluation of unexplained elevated AST, ALT should include testing for celiac disease


Dermatitis Herpetiformis

- Pruritic papulovesicular lesions
  - IgA deposits at dermal-epidermal junction
- Almost all have abnormal intestinal biopsies
  - Few have GI symptoms
- Treatment directed against skin doesn’t help gut lesions (e.g., dapsone)
- Gluten free diet helps both gut and skin

Histopathology of DH

Hematoxylin & eosin staining  Immunofluorescent staining

Associated Autoimmune Conditions

- Diabetes mellitus - Type I
  - ~ 3 to 8% have celiac disease
- Autoimmune thyroid disease (~5%)
- Addison’s disease
- Alopecia areata
- Sjogren’s syndrome
- Others
Obstetrical & Gynecological Presentations in Untreated CD

Patients with untreated celiac disease sustain:
- Delayed menarche
- Earlier menopause
- Increased prevalence secondary amenorrhea
- Infertility
- Higher miscarriage rates (9-fold increase)
- Increased IUGR
- Lower birth weights
- Premature births

Reviewed in Eliakim & Sherer, Gynecol Obstet Invest, 51: 3, 2001

Associations or Presentations: Neuropsychiatric & Behavioral

- Hyperactivity - attention deficit disorder??
- Irritability
- Cognitive deficits
- Cerebral calcifications
- Fatigue
- Seizures
- Peripheral neuropathy
- Ataxia
- Myelopathy
- Schizophrenia
- Depression
- Migraines
- Autism??

Screen for celiac disease in unexplained ataxia or peripheral neuropathy

Silent and Latent Celiac Disease

- Both forms bear HLA haplotypes associated with celiac disease and have abnormal serology
- Silent or Asymptomatic CD - abnormal intestinal histology but no recognized clinical manifestations
- Latent or Potential CD - normal histology
  - Increased yield of diagnostic tests after gluten challenge
  - serology (EMA, TTG)
  - biopsy findings (increased IEL)
- Genetically at risk – have only HLA susceptibility genes
- Natural history of silent or potential CD forms is unknown
- How to manage these cases is therefore unclear
- Usually detected through screening

Diagnosis

- Characteristic histological findings
- Clinical, serological, and in some cases, histological response to a gluten free diet
- Rarely necessary to observe clinical and histological response to gluten challenge
- Intestinal biopsies are the only method by which celiac disease can be diagnosed
- However, for dermatitis herpetiformis a classical skin biopsy is often sufficient


Serologic Tests in Adults - 2004

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA IgA</td>
<td>&lt; 80% in 50%</td>
<td>&gt; 80% in most</td>
</tr>
<tr>
<td>AGA IgG</td>
<td>variable</td>
<td>non-specific</td>
</tr>
<tr>
<td>EMA IgA</td>
<td>96-97% ME, 90% HUV</td>
<td>100% ME, HUV</td>
</tr>
<tr>
<td>TTG IgA</td>
<td>90% GP, 98% HR</td>
<td>95% GP, 98% HR</td>
</tr>
<tr>
<td>TTG IgG</td>
<td>40%, but higher in IgA deficiency</td>
<td>98%</td>
</tr>
</tbody>
</table>

Rostom et al, Gastroenterology, 128:538, 2006

Performance of Diagnostic Tests for Identifying Celiac Disease - 2010

- 16 studies included (N=6085 subjects)
- EMA IgA (N=8 studies)
  - Sensitivity 0.90 (95% CI, 0.80-0.95)
  - Specificity 0.99 (95% CI, 0.98-1.00)
- TTG IgA (N=7 studies)
  - Sensitivity 0.89 (95% CI, 0.82-0.94)
  - Specificity 0.98 (95% CI, 0.95-0.99)

TTG IgA and EMA IgA have high sensitivity and specificity for diagnosing celiac disease in adults with abdominal symptoms in primary care or other unselected populations

Van der Windt et al., JAMA, 303:1738, 2010
Serum from celiac with active disease preferentially recognize deamidated gliadin peptides

IgA and IgG antibodies to deamidated gliadin peptides (DGP) are more sensitive and specific tests than IgA and IgG antigliadin antibodies (AGA)

Deamidated Gliadin Peptide (DGP) Abs

What are the Best Serological Tests for Screening?

- Depends on prevalence and age of population being examined
- Overall, TTG IgA is the recommended test to screen for disease but sensitivity varies with lower levels (≤90%) reported in routine practice, 1 in 10 false negative rate
- Check total IgA for assays with narrow range of normal
- EMA IgA is helpful when positive
- TTG, EMA less sensitive for milder histologic stages
- Traditional AGA no longer used as a first line antibody test except in young children
- Antibodies to GDP are less sensitive than to TTG

Endoscopic Findings in Celiac Disease

- Flattened or absence of folds
- Notching or scalloping of folds
- Fissuring of mucosa

Endoscopic findings are not very sensitive but they are quite specific

If you suspect celiac disease, take biopsies!

Celiac Disease

Immune disorder in which gluten causes intestinal damage

Enteropathy defines celiac disease

To enhance detection take ≥6 biopsies including at least one from the duodenal bulb

Spectrum of Histopathology

Marsh II (modified 2)  Marsh IV (modified 3c)

Number of Specimens and Probability of Diagnosing Celiac Disease

Proposed New Criteria for Diagnosis

“Four out of five” sufficient to diagnose CD?

- Typical symptoms of CD
- High titer of serum CD IgA class autoantibodies
- HLA DQ2 and/or HLA-DQ8 genotypes
- Celiac enteropathy by small bowel biopsy
- Response to a GFD

This proposal remains controversial amongst other experts in the field.

When to Use Genetic Testing

- How to test:
  - PCR of RNA extracted from cells in a cheek swab or blood sample
- Who to test:
  - Close relatives of patients with confirmed CD wishing to know if they are at risk of developing CD
  - Patients on a gluten free diet who are candidates to undergo a gluten challenge to confirm possible CD
  - Equivocal histology and serology findings in which a negative test result would make CD highly unlikely
- How often to test: Once in a lifetime

Dietary Response to a Gluten Free Diet: Is this Diagnostic?

- Placebo response in IBS up to 70%
- Gluten (increased prolamines) is hard to digest, increases stool volume
- Gluten free diet often eliminates other dietary factors
- Potentially other mechanisms explain benefit
- PPV of symptom improvement after gluten withdrawal for celiac disease only 36% in one study

What is Gluten Sensitivity?

<table>
<thead>
<tr>
<th>Oslo Definitions</th>
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<tr>
<td>Gluten Sensitivity Due to Celiac Disease (CD)</td>
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<tr>
<td>Non-Celiac Gluten Sensitivity (NCGS)</td>
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Between Celiac Disease & IBS: The “No Man’s Land” of Gluten Sensitivity

Gluten Causes Symptoms in IBS Patients Without Celiac Disease

Adverse Reactions to FODMAPs

Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols
- Fructose and fructans
- Sorbitol
- Sucrose
- Lactose
Many foods (grains including wheat starch, fruits, vegetables) contain FODMAPs

No Effect of Gluten after Reduced FODMAP Diet in IBS Patients

• 37 subjects with IBS (Rome III) reporting NCGS (celiac disease meticulously excluded) underwent double-blind cross-over study
• 2 wks low FODMAP diet resulted in significant improvement of GI symptoms and fatigue
• Challenge with gluten (high, low or control) did not result in symptomatic or biological changes
• Suggests sensitivity may not be due to gluten

Gluten Coexists with Nonabsorbed Fructans and Other Saccharides

**Putative Mechanisms of NCGS**

- Elevated AGA IgA, IgG (up to 50% + AGA IgG)
- No specific HLA association
- Some studies suggest gluten may activate the innate immune system (IL-8, IFN-γ, etc) in NCGS
- Increased permeability, mucosal inflammation, basophil activation but not found in a recent study
- Other proposed mechanisms include immune complex, autoimmune, microbiota, wheat amylase trypsin inhibitors, toxicity, false neurotransmitters, leaky gut.


**Possible Mechanisms of Wheat Sensitivity in IBS and other FGID**

- Innate immune reaction to gluten
- IgE mediated wheat allergy
- Non-Celiac Wheat Intolerance
- Low grade inflammation
- Opioid-like activity of gluten
- Starch/CHO Malabsorption
- Nocebo effect

**Proposed Mechanisms of Non-Celiac Gluten or Wheat Sensitivity**

- Wheat ingestion
- Poorly Absorbed Carbohydrates
- Gas production & SCFA formation
- Altered Permeability
- Immune Activation/
- Low grade inflammation
- GI Symptoms

- SCFA = short chain fatty acids

**Gluten Free Market**

The market for gluten-free food and beverage products grew at a compound annual growth rate of 28 percent from 2004 to 2008, to finish with almost $1.6 billion in retail sales. By 2012 sales were expected to reach $2.6 billion.

Sales are now predicted to be $1.68 billion in the USA and $3.38 billion worldwide by 2015 (Reuters on line, Sept 2012)

**Patients Already on a Gluten Free Diet: How to Test for Celiac Disease**

- Depends on duration and stringency of the GFD
- If truly on a GFD for years it is difficult to prove CD
- Many patients on a self-taught GFD are not truly gluten-free
- Serology can take over a year to normalize
- Histology can take several years plus to become normal
- Thus, if an undiagnosed patient wants an assessment for possible CD assets with serological tests, HLA DQ2/8 and EGD with biopsies within the first year on a GFD
- Absence of HLA DQ2.2, 2.5 or 8 effectively excludes CD now or in the future

**What to Do with the Patient on a Gluten Free Diet without Biopsy?**

- Celiac disease is possible & patient is willing to undergo gluten challenge?
  - Up to 6 to 12 months on “GFD” check serology and consider EGD + Bx
  - Yes, get genetic testing
  - No but wants genetic testing for sake of children
  - Positive – increases likelihood of celiac disease, encourage gluten challenge
  - No further evaluation if they will still stay on GFD regardless of evaluation and will not have children tested
  - Negative – not celiac disease, still use GFD for symptom control only

- Check Ab q1-2 months up to 6 months
- EGD + Bx if Ab +, symptoms develop, or by 3-6 months
- Low fat diet low carb diet gluten free diet

- Genetic testing for HLA DQ2/2.5 and 8.
- Full blood count, liver enzymes, vitamin B12, and ferritin levels.
- If serology is positive, order serologies and AGA and/or EGD + Bx.

**What Studies Should Be Considered in the Evaluation of the Patient?**

- EGD + Bx: If Ab +, symptoms develop, or by 3-6 months
- No but wants genetic testing for sake of children
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Gluten Challenge
• Gradual increase of gluten up to target (ideally 10g equivalent of 4 slices bread/day but varies by patient)
• One study showed that a 14-day 3 g challenge was sufficient to induce serologic and histologic changes
• Check TTG IgA 2-6 weeks until positive
• EGD/biopsy if diarrhea develops and/or seropositive
• Management if still seronegative at 3 to 6 months needs to be individualized but typically involves EGD/biopsy now or after longer gluten challenge

Management
• Goal: Return to normal health and prevent complications of untreated celiac disease
• Life-long gluten free diet
• Low lactose diet initially
• Nutritional supplements if deficient
  – Calcium, vitamin D, iron, folate and other nutrients
• Refer to a knowledgeable nutritionist
• Encourage patients to join local chapters of various celiac organizations, gain knowledge

Selected Resources for Patients with Celiac Disease and Their Families

Websites
• Celiac Disease Foundation (CDF), www.celiac.org
• Gluten Intolerance Group of NA (GIG), www.gluten.net
• National Foundation for Celiac Awareness, www.celiaccen.org
• Canadian Celiac Association (CCA), www.celiac.ca
• Celiac Sprue Association, www.csaceliacs.org

Books
• Case, Shelley, The Gluten Free Diet, 2010
• Blumer, I. & Crowe, Sheila, Celiac Disease for Dummies, Wiley, 2010
• Dennis, M., Leffler, D ed. Real Life with Celiac Disease: Troubleshooting and Thriving on a Gluten Free Diet, AGA Institute Press, 2010

Treatment = Gluten Free Diet
• Non-compliance is an issue
  – Eating out of the home
  – Peer pressure for children, teens
  – Less acceptable taste, texture of foods
  – Accidental ingestion of gluten
  – Cost (3 times higher), availability, labeling
• GF diet may ameliorate complications of the disease
• Unclear how much gluten, if any, is safe
  – New FDA guidelines 20 ppm (up to 10 mg/day safe)
  – Labeling in USA for wheat since 2006, gluten since 2008

Why a Gluten Free Diet?
• Probably benefits overall cancer risk (Leffler & Loftus, Gastroenterology, 132:775, 2007)
• Improves unexplained infertility and pregnancy outcomes (Leffler et al, Gut, 50:109, 2001, many other studies)
• Ameliorates osteoporosis
• Corrects iron deficiency
• Improved QOL even for those detected by screening (Mustalhi, E, Eff Clin Pract, 5:503, 2002)
• However, studies report decreased QOL adhering to a GFD
  – GFD is beneficial for preventing, reversing and/or treating some complications

Follow-up of Patients with Celiac Disease
No established or EB guidelines yet
• Correct nutritional deficiencies
• Follow TTG IgA until it is normal
• Consider checking TTG IgA every 1-2 years thereafter
• Repeat DEXA scan every 2 years if abnormal
• In some instances repeat EGD with biopsy
• Promote general good health (exercise, cease smoking, maintain normal BMI, adhere to screening guidelines)
Summary of CD, NCGS and Other Sensitivity to Wheat

- Celiac disease (CD) is not rare (1 in 100-300)
- CD can coexist with or mimic IBS and other FGID
- New therapies for CD in development or trials
- Increased reporting of NCGS, prevalence unknown
- Cannot clinically differentiate NCGS and CD
- Gluten free diet remains the mainstay of therapy for both conditions
- How GS contributes to FGID remains unclear but multiple mechanisms implicated
- Other forms of wheat intolerance are emerging
- Additional research is needed! Stay tuned....