Celiac Disease & Non-Celiac Gluten Sensitivity

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Case Scenario
- 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 and should get herself tested

Case Scenario
- “Doc – what is celiac disease?”

Celiac Disease
- Pathophysiology
- Prevalence
- Presentation
- Diagnosis
- Mortality & Morbidity
- Treatment

Non-celiac Gluten Sensitivity
Celiac Disease

- “What is celiac disease?”
  - Chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals

Pathogenesis of Celiac Disease: Gluten

- Wheat
- Rye
- Barley

Shan Science 2002

Green, NEJM 2007.
Genetic Factors: HLA-DQ2/HLA-DQ8

- 25-30% Caucasian population DQ2/8 positive
- 4% of DQ2/8 positive individuals exposed to gluten develop CD


Pathogenesis of Celiac Disease

Host
- HLA:DQ2/DQ8
- Non HLA genes

Triggers
- Wheat
- Barley
- Rye

Cofactors
- Intestinal Infections
- Infant feeding practices
- Socioeconomic factors

Di Sabatino, Lancet 2009

Incidence of celiac in active duty US military

“Incidence of CD diagnosis in a healthy US adult population is increasing…and appears higher than other population-based estimates”

Riddle. AJG 2012

Environmental Risk Factors: CD diagnosis up 4-fold

- Analysis of stored blood samples, taken from Air Force recruits in the early 1950s, for TTG and if positive, EMA.
  - 0.2% positive - celiac disease was “rare”
- 2 more recently collected sets from Olmsted County, Minnesota.
  - 0.8-0.9%
- Their findings suggest that CD is roughly 4 times more common now than in the 1950s

Rubio-Tapia Gastro 2009
Environmental Risk Factors: Infections

- Rotavirus infection an independent risk factor for celiac disease
  - Changes the permeability of and the cytokine balance in the intestinal mucosa
- Influence of other common infections not yet clarified
  - Riddle et al: association between antecedent infectious gastroenteritis and risk of CD; strongest in non-viral IGE.
- Gut microbiota:
  - Nadal et al: higher incidence of Gram-negative and potentially pro-inflammatory bacteria in the duodenal microbiota of CD children


Environmental Risk Factors: Infant feeding

- Swedish epidemic:
  - 3x higher CD prevalence with change in national recommendations
- ESPGHAN: small amounts of gluten, gradually introduced between 4-7 months of age during breastfeeding

Environmental Risk Factors: Infant feeding

- Potential mechanisms:
  - Immunomodulatory activity:
    - ↑bifidobacteria
    - ↓infection
  - Amount of gluten introduced

Nadal, J Med Microbio 2007; Silano WJG 2010

Environmental Risk Factors: Socioeconomic Factors

- Russian Karelia vs. Finland
  - TTG ale: 0.6% versus 1.4% (P=.005)
  - Biopsy proven CD:
    - Prevalence of 1 in 496 Karelian children compared to 1 in 107 Finnish children
- Remote territory of Russia – “They live like Finns 50 years ago.”

Environmental Risk Factors: Socioeconomic Factors

- Analysis of house dust and potable water:
  - Russian Karelians encountered a greater variety and quantity of microbes, including many that were absent in Finland.
- Worse conditions might protect against CD
  - Variations in gut flora
  - Infections – hygiene hypothesis

Velasquez-Manoff, NYT 2013

Case Scenario

- “How common is it?”

Celiac Disease Prevalence

- “How common is it?”
  - US: 1:100 (range 1:80 to 1:140)
    - Estimated that less than 5% of those with CD in the US are currently diagnosed

Green AJG 2007

Which region has the highest known prevalence of celiac disease?

1. North America
2. South America
3. Europe
4. Asia
5. Africa
6. Australia
### Celiac Disease Prevalence

<table>
<thead>
<tr>
<th>Country</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>0.18-2.0%</td>
<td>0.2-1.3%</td>
</tr>
<tr>
<td>Germany</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Great Britain</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Finland</td>
<td>0.5-2.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Italy</td>
<td>0.7</td>
<td>0.54-0.85</td>
</tr>
<tr>
<td>Russia</td>
<td>0.2</td>
<td>NA</td>
</tr>
<tr>
<td>North and South America</td>
<td>0.15-2.6</td>
<td>0.9%</td>
</tr>
<tr>
<td>Mexico</td>
<td>2.6</td>
<td>NA</td>
</tr>
<tr>
<td>USA</td>
<td>0.4-0.9%</td>
<td>NA</td>
</tr>
<tr>
<td>Asia</td>
<td>0.6-1.6</td>
<td>0.02-1.0</td>
</tr>
<tr>
<td>India</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>Syria</td>
<td>1.6</td>
<td>NA</td>
</tr>
<tr>
<td>Africa</td>
<td>0.28</td>
<td>0.64-5.6</td>
</tr>
<tr>
<td>Algeria</td>
<td>NA</td>
<td>5.6</td>
</tr>
<tr>
<td>Tunisia</td>
<td>0.28</td>
<td>0.64</td>
</tr>
</tbody>
</table>

North and South America

Mexico 2.6 NA
USA 0.4-0.9 NA
Asia 0.6-1.6 0.02-1.0
India NA 1.0
Syria 1.6 NA
Africa 0.28 0.64-5.6
Algeria NA 5.6
Tunisia 0.28 0.64


### Celiac Disease Prevalence: "New Epidemiology"

- Saharawi children
  - Highest known prevalence of CD
  - Genetic factors: high frequency of HLA DQ2
    - Arabic and Berber ancestry
  - Environmental factors:
    - live as refugees in Algeria
    - rates and duration of breast feeding reduced
    - large amount of wheat consumption in early life – humanitarian aids from western countries

Cataldo, WJG 2007

Frontiers in celiac disease, 2008. Edited by A. Fasano, Riccardo Troncone, D. Branski
Celiac Disease Prevalence: “New Epidemiology”

- Northern India – Punjab
  - Genetic predisposition – Aryan descent with HLA-predisposing genes
  - Environmental factors
    - “summer diarrhea”
    - Wheat typical staple food (chapattis, roti)
  - winter – maize (makhi roti)

- Genetic predisposition – Aryan descent with HLA-predisposing genes

- Environmental factors

- "summer diarrhea"
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  - winter – maize (makhi roti)

Cataldo, WJG 2007

Celiac Disease Prevalence: “New Epidemiology”

- Worldwide public health problem
- Involves all ethnic groups in all the areas of the world where there is great consumption of wheat
  - “westernization” diet
  - Humanitarian interventions

Cataldo, WJG 2007

Celiac Iceberg

- Total size of the iceberg is more or less the same in most parts of the world
- The ratio of diagnosed to undiagnosed cases of CD is thought to be highly variable
  - 1:2 in Finland
  - 1:20 in US
- Most cases undetected

WGO Celiac Guidelines 2012
**Detection of CD in Primary Care**
- Survey of adult celiac patients in USA
  - Majority dx in 4th – 6th decade
  - Symptoms present a mean of 11yrs 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 20yrs
  - Only 35% had ever diagnosed a pt with CD

**Celiac Disease: a systemic disease**
- General
  - Growth delay
- GI
  - Diarrhea, malabsorption
  - Constipation
  - hepatitis
- Skin:
  - Dermatitis herpetiformis

**Dermatitis Herpetiformis**
- Cutaneous manifestation of gluten sensitivity
- Extensor surfaces of the elbows, knees, buttocks, and back
- Pruritic

**Celiac Disease: a systemic disease**
- General
  - Growth delay
- GI
  - Diarrhea, malabsorption
  - Constipation
  - hepatitis
- Skin:
  - Dermatitis herpetiformis
- Metabolic bone disease
- Neurologic
  - Depression, epilepsy, migraine
  - Gluten ataxia
- Endocrine
  - Type 1 DM, thyroid disease
- Cardiovascular
- Infertility
High Risk Populations

- Relatives: 10%
- Fe deficiency 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).

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

- Multicenter, prospective study 2002-2004
- Questionnaire to individuals over 18y soliciting:
  - Symptoms
    - Diarrhea
    - Abdominal pain, constipation
    - Chronic fatigue
    - Infertility
    - Epilepsy or ataxia
  - Abnormal lab values
    - Anemia
    - LFTs
  - Associated diseases
    - IBS
    - Autoimmune
    - Down’s syndrome
    - Turner’s syndrome
    - Family h/o celiac disease

Detection of CD in Primary Care:

- 38% (976/2568) responded affirmatively 1+ items
- CD diagnosed in 2.25% (22/2568)
  - Most frequent reason: bloating (12), thyroid disease (11), IBS (7), unexplained chronic diarrhea (6), chronic fatigue (5), constipation (4)
- Following implementation of active screening
  - 32-43 fold increase in diagnosis of CD

CD: Trends in presentation
Case Scenario

“How do we diagnose it?”

Serology

- IgA tTG: preferred single test
- IgA EMA: more time consuming, operator dependent
- IgA deficiency: 2-3% patients with CD

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA anti-tTG</td>
<td>98%</td>
<td>98%</td>
<td>72%</td>
<td>99%</td>
</tr>
<tr>
<td>EMA IgA</td>
<td>95%</td>
<td>99%</td>
<td>83%</td>
<td>99%</td>
</tr>
<tr>
<td>IgG anti-tTG</td>
<td>70%</td>
<td>95%</td>
<td>42%</td>
<td>99%</td>
</tr>
<tr>
<td>IgA/IgG anti-DGP</td>
<td>97%</td>
<td>95%</td>
<td>51%</td>
<td>99%</td>
</tr>
</tbody>
</table>

Serology

Leffler AJG 2010

Endoscopy with Biopsy for Diagnosis:

- Endoscopic sings:
  - Decrease in duodenal folds
  - Scalloping of folds
  - Mucosal fissures
  - Nodularity
- 4-6 biopsies
  - Including duodenal bulb

Pathological Diagnosis

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

Celiac Disease & Non-Celiac Gluten Sensitivity

- Celiac Disease
  - Pathophysiology
  - Prevalence
  - Presentation
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  - Mortality & Morbidity
  - Treatment
- Non-celiac Gluten Sensitivity

Case Scenario

- “Will I get cancer? Am I going to die from it?”

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


Mortality and CD

- SMR: 1.9 – 3.4
- Risk of death higher among patients with severe presentation
  - Presenting with malabsorption (SMR 2.5)
  - Not adhering to GFD (SMR 10.7)
  - Diagnostic delay

Mortality in Celiac Disease

- Dominant cause of death:
  - Cardiovascular death: 20% increased risk
    - increased risk of ischemic heart disease, stroke, atrial fibrillation and potentially also autoimmune heart disease
  - Malignancy
  - GFD appears protective
    - Adherence: no excess mortality
    - Unlikely to comply: SMR 2x higher
    - Definitely noncompliant: SMR 6x higher
  - SMR correlated to severity of presentation
  - Risk of mortality decreased over time

Mortality in Undiagnosed Celiac Disease

- Study results variable
- Ab screen on stored serum samples, matched to mortality data
- Four studies: no increased mortality (UK, Finland, US elderly)
- Two studies: SMR 2.53 -4 (Germany, USA)

Mortality in Undiagnosed Celiac Disease

- 9133 healthy young adults at Warren Airforce Base
- TTG, anti-endomysial ab testing
- During 45 years of follow-up, undiagnosed CD was associated with a nearly 4-fold increased risk of death.
Morbidity in Undiagnosed Celiac Disease

- Undiagnosed maternal celiac disease
  - ↑ risk of infertility, spontaneous abortions
  - ↑ preterm birth and cesarean section rates
  - negative effect on intrauterine growth/birth weight
- Associated with increased fracture risk
- Associated with increased risk of lymphoma and small bowel cancer
  - although overall rates are low

Common Pitfalls in Diagnosis of CD

- Gluten reduced diet may reduce sensitivity of serological screening and the severity of lesion on pathology
  - Negative test in the setting of GFD not conclusive
- 4-6 week challenge with “sufficient” gluten
  - ACG: 3g gluten challenge for 2 and then 6 weeks

Case Scenario

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

Case Scenario

- “No way am I going back on a gluten diet…”
**HLA-DQ2 and DQ8**

- Sensitivity 100%
  - Absence of these alleles provides a NPV close to 100%
- Poor specificity
  - Approximately 25%–40% of the general population in the United States carry the HLA class II heterodimer HLA-DQ2 or HLA-DQ8
- Necessary but not sufficient for diagnosis of CD

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**Celiac Disease & Non-Celiac Gluten Sensitivity**

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**Gluten Free Diet (GFD)**

- Gluten Free Diet (GFD)
  - Only effective treatment for CD
  - Avoidance of wheat, rye, barley
    - Found in bread, biscuits, cakes, pastries, breakfast cereals, pasta, beer and most soups, sauces (including soy sauce), and puddings
  - Supplements, medications
  - Registered Dietician

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**GFD**

- Green, NEJM 2007; AGA Celiac Guidelines 2015.
Monitoring Celiac Disease

- Patients with celiac disease should be evaluated at regular intervals by a health care team including a physician and a dietician.
- Repeat serologic testing after 3-6 months on a GFD
  - the serologic test results tend to become negative as the histologic findings improve
    - 80% at one year; 99% at 5 years
  - sensitivity for minor dietary indiscretion can be LOW
- Followed at least annually


Monitoring Celiac Disease

- Screen for nutritional deficiencies
  - calcium, vitamin D
  - Iron
    - CBC
  - Vitamin A, E, INR
  - LFTs, albumin
  - Vitamin B12, Folate

ACG Celiac Guidelines 2013

Management of Celiac Disease

- Cardiovascular prevention:
  - Cessation of smoking
  - Treatment of hypertension
  - Treatment of hyperlipidemia
  - Encouraging physical activity
  - Avoiding obesity: Dickey AJG 2006 - 39% overweight @ dx
- Metabolic bone disease: DEXA
- Thyroid disease: TSH
- Hyposplenism: prophylactic pneumococcal vaccination


Celiac Disease

- Pathophysiology – gaps in knowledge
- Prevalent disease with associated morbidity and mortality
- Diverse populations
- Diverse presentations
- Screening: sensitive and specific serology
- Treatment is effective, low risk/ high benefit
Celiac Disease & Non-Celiac Gluten Sensitivity

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  - Treatment
- Non-celiac Gluten Sensitivity

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Case 2

- 64yo male with extensive work up for abdominal pain, gas/bloating, negative for celiac disease (negative serology, negative biopsy), but insistent that he cannot tolerate gluten.

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Gluten Goodbye: One-Third Of Americans Say They're Trying To Shun It

- "Right now 29 percent of the adult population says, 'I'd like to cut back or avoid gluten completely’"
- NPR, March 9 2013 by Nancy Shute

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Non-Celiac Gluten Sensitivity

- IBS- like symptoms occurring after the ingestion of gluten
  - Abdominal pain, bloating, diarrhea, flatulence
- Negative celiac serology, normal histology
- Ruled out wheat allergy (skin prick, serum IgE)
- Symptoms disappear after gluten is withdrawn from the diet
- Symptoms re-present after double blind placebo controlled gluten re-challenge

Non-Celiac Wheat Sensitivity Diagnosed by Double-Blind Placebo-Controlled Challenge: Exploring a New Clinical Entity

OBJECTIVES: Non-celiac wheat sensitivity (WS) is considered a new clinical entity. An increasing percentage of the general population avoids gluten ingestion. However, the real existence of this condition is debated and specific markers are lacking. Our aim was thus to demonstrate the existence of WS...

Double blind placebo controlled trial

Non-celiac Wheat Sensitivity

1/3 of IBS patients who underwent DBPC wheat challenge were really suffering from WS.

Two groups of patients:
- 70/920 (7.6%): suffering from WS alone - characterized by clinical features similar to those found in CD patients
- 206/920 (22.3%): suffering from multiple food sensitivity - characterized by clinical features similar to those found in allergic patients.
Non-Celiac Gluten Sensitivity

- “We do not have a biomarker, we do not know the mechanisms, we do not have reliable epidemiological data that tell us how many patients who believe they are affected by nonceliac gluten sensitivity really have this condition.”


Non-Celiac Gluten Sensitivity

- Does not have a strong hereditary basis
- Not associated with malabsorption or nutritional deficiencies
- Not associated with any increased risk of autoimmune disorders or intestinal malignancy

* Implications for disease monitoring, required duration and strictness of adherence to GFD, counseling and testing of family members

ACG Celiac Guidelines 2013.

Gluten Free Diet

- Difficult:
  - Food availability
  - Food contamination
- Expensive
  - Canadian study: gluten-free products 242% more expensive
- Potential nutritional deficiencies


Gluten Free Diet: Deficiencies

- fiber
- iron
- folate
- B complex vitamins
- calcium
- magnesium
- vitamin A
- zinc
- riboflavin

Shepherd, J H Nutrition & Dietetics 2012
Gluten Free Diet: Deficiencies

- fiber
- iron
- folate
- B complex vitamins
- calcium
- magnesium
- vitamin A
- zinc
- riboflavin

*Oats improves the nutrient content of GFD


GFD: Weight Gain

- At diagnosis: 90% of the study population were at normal weight or with a body mass index (BMI) > 20
- 81% of the population gained weight when on the gluten-free diet.
  - Of the study population that was obese, 82% gained more weight

Dickey AJG 2006


Potential therapeutic targets

McAllister Seminol Immunopath 2012

Clinical and Pathogenic Differences among Celiac Disease, Gluten Sensitivity, and Wheat Allergy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Celiac Disease</th>
<th>Gluten Sensitivity</th>
<th>Wheat Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval between exposure to gluten and onset of symptoms</td>
<td>Weeks to years</td>
<td>Hours to days</td>
<td>Minutes to hours</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Autoimmunity ( innate and adoptive immunity )</td>
<td>Possibly innate immunity</td>
<td>Allergic immune response</td>
</tr>
<tr>
<td>HLA</td>
<td>Restricted to HLA-DQ2 or HLA-DQ8 (in approximately 95% of patients)</td>
<td>Not restricted to HLA-DQ2 or HLA-DQ8 (HLA-DQ2-positive, or both in 100% of patients)</td>
<td>Not restricted to HLA-DQ2 or HLA-DQ8 (HLA-DQ2-positive, or both in 30% of patients, similar to the general population)</td>
</tr>
</tbody>
</table>


Non-celiac Gluten Sensitivity: Pathogenesis