Coeliac Disease, Wheat Allergy & Non-Celiac Gluten Sensitivity

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Outline:

- Gluten related disorders are increasingly common
- Celiac disease (CD) and Non-Celiac gluten Sensitivity (NCGS) defined
- Diagnostic Testing for CD versus NCGS
  - Celiac serologies
  - Celiac gene testing
  - “Gluten challenge”
The World View of Celiac Disease circa 1990

North America
CD Rare
1/5000

Ireland
1/300

Europe
1/1000

South America
CD Very Rare
1/????

Africa
Asia
CD very Rare

Kelly CP. Celiac Disease & Refractory Celiac Disease. Sleisenger & Fordtran’s GI & Liver Disease, 10th edition, 2015
# Celiac disease at BIDMC/Harvard, Boston

## Patient and Visit Volumes since 1997

<table>
<thead>
<tr>
<th>Year</th>
<th>Patient Visits</th>
<th>Fold increase</th>
<th>Individual Patients Treated</th>
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</thead>
<tbody>
<tr>
<td>1997</td>
<td>47</td>
<td>1</td>
<td>38</td>
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<tr>
<td>1998</td>
<td>167</td>
<td>4</td>
<td>125</td>
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<td>1999</td>
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<td>3</td>
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<td>2000</td>
<td>136</td>
<td>3</td>
<td>102</td>
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<tr>
<td>2001</td>
<td>160</td>
<td>3</td>
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<td>2002</td>
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<td>2003</td>
<td>590</td>
<td>13</td>
<td>304</td>
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<td>2004</td>
<td>698</td>
<td>15</td>
<td>370</td>
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<tr>
<td>2005</td>
<td>919</td>
<td>20</td>
<td>471</td>
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<tr>
<td>2006</td>
<td>1,336</td>
<td>28</td>
<td>615</td>
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<td>2007</td>
<td>1,720</td>
<td>37</td>
<td>780</td>
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<tr>
<td>2008</td>
<td>2,034</td>
<td>43</td>
<td>928</td>
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<tr>
<td>2009</td>
<td>2,118</td>
<td>45</td>
<td>1,016</td>
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<tr>
<td>2010</td>
<td>2,137</td>
<td>45</td>
<td>1,058</td>
</tr>
<tr>
<td>2011</td>
<td>2,257</td>
<td>48</td>
<td>1,088</td>
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<td>2012</td>
<td>2,576</td>
<td>55</td>
<td>1,222</td>
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**Note:** IgA-TTG use increases.
Today’s World View of Celiac Disease
Common & Not Limited to Europeans

- Americas & Europe: ~1% (0.6 to 2.5%)
- Finland: ~2.5%
- Northern India: 1 to 3%
- SouthEast Asia: CD Rare?
- Subsaharan Africa: CD Rare
- Australia: ~1.5%

Kelly CP. Celiac Disease & Refractory Celiac Disease. Sleisenger & Fordtran’s GI & Liver Disease, 10th edition, in press
Increased Prevalence Over Time in U.S.A. 
(in Line with Other Autoimmune Diseases)

During the past 35 years the true prevalence of CD in USA doubled every 15 years.

C. Catassi et al, Annal Med (on line ahead of print)
Why is celiac disease more common?

Why are many “auto-immune” and allergic conditions increasingly common?

• **Hygiene theory**
  - Our immune system developed to constantly fight germs and parasites
  - Modern hygiene leads it to react against harmless environmental antigens and auto-antigens

“An idle immune system is the devil’s playground”
Gluten Related Disorders
## Gluten & wheat related disorders

<table>
<thead>
<tr>
<th>Celiac disease</th>
<th>Non-celiac Gluten Sensitivity (NCGS)</th>
<th>Wheat allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>~1% of population</td>
<td>&gt; 1% (0.6-30%) of population</td>
<td>&lt; 1% of population</td>
</tr>
<tr>
<td>• Positive IgA tTG antibody test</td>
<td>Symptoms on gluten exposure [after allergy and celiac disease excluded]</td>
<td>• Food allergy symptoms</td>
</tr>
<tr>
<td>• Abnormal biopsy</td>
<td></td>
<td>• Positive RAST / skin test</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other food allergies</td>
</tr>
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</table>
Oslo Definitions for Gluten Related Disorder

- **Celiac disease (CD)** is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals.

- **Non-Celiac Gluten Sensitivity (NCGS)** relates to one or more of a variety of immunological, morphological or symptomatic manifestations that are precipitated by the ingestion of gluten in people in whom CD has been excluded.

*Gluten-related disorders* is the suggested umbrella term for all diseases triggered by gluten

Non-Celiac Gluten Sensitivity

- NCGS not a new entity, reported in 1980
  - Reported in association with allergic diseases
- True prevalence unknown but probably greater than celiac disease
  - Varies from 0.548% (NHANES) to 30%
  - Studies reporting prevalence reflect referral bias

Non-celiac gluten sensitivity

Gluten Causes Gastrointestinal Symptoms in Subjects Without Celiac Disease: A Double-Blind Randomized Placebo-Controlled Trial

Similar & significant differences for: Abdominal pain, bloating, tiredness & satisfaction with stool consistency

1. NCGS is a real phenomenon
2. Celiac disease cannot be diagnosed by a trial of GFD
Is Gluten the Culprit After All?

37 subjects with NCGS and irritable bowel syndrome

Double blind RCT
• 2-week diet of reduced FODMAPs followed by one of the following:
  • high-gluten (16 g gluten/d)
  • low-gluten (2 g gluten/d and 14 g whey protein/d)
  • control (16 g whey protein/d)

Results:
• GI symptoms improved with ↓FODMAP intake, worsened with gluten or whey protein intake
  – Gluten-specific effects in only 8%

➢ Little evidence of specific gluten effects in patients with NCGS placed diets low in FODMAPs.

FODMAP = fermentable, oligo-, di-, monosaccharides, and polyols
Process of Elimination

To determine if certain foods are triggering symptoms of irritable bowel syndrome, some specialists recommend a low-Fodmaps diet, which stands for Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols. After six to eight weeks, the foods are gradually reintroduced at low levels to see what patients can tolerate.

**SOME FOODS CONTAINING FODMAPS TO ELIMINATE:**

**FRUIT**
- Apples
- Apricots
- Cherries
- Pears
- Watermelon
- Dried Fruit

**VEGETABLES**
- Asparagus
- Broccoli
- Cabbage
- Eggplant
- Garlic
- Mushrooms
- Onions

**CEREALS / GRAINS**
- Wheat, rye in large quantities
- Pasta
- Bread
- Cookies

**MILK PRODUCTS**
- Cow’s milk
- Custard
- Ice cream
- Yogurt
- Soft cheeses

**OTHER**
- Sweeteners: sorbitol, mannitol, isomalt
- Fructose, corn syrup, honey

**BEANS / LEGUMES**
- Chick peas
- Kidney beans
- Lentils
- Soy beans

**SOME SUITABLE FOODS ON A LOW-FODMAP DIET:**

**FRUIT**
- Bananas
- Blueberries
- Grapefruit
- Lemons
- Raspberries

**VEGETABLES**
- Carrots
- Celery
- Green beans
- Potatoes
- Pumpkin
- Zucchini

**GRAINS**
- Gluten-free bread or cereal
- Rice
- Oats
- Polenta
- Tapioca

**MILK PRODUCTS**
- Lactose-free milk and yogurt
- Hard cheeses

**OTHER**
- Tofu
- Sugar
- Maple syrup
- Molasses

Proposed Mechanisms for NCGS

Wheat ingestion

- Poorly Absorbed Carbohydrates
- Gluten-mediated
- Nocebo Effect
- Altered Permeability
- Immune Activation/Low grade inflammation
- Gas production & SCFA formation
- Microbiome changes

GI Symptoms

SCFA = short chain fatty acids

Vazquez-Roque MI, et al. Gastroenterology 2013;144:903
Non-celiac Gluten Sensitivity, Celiac disease, IBS & Dysbiosis are inter-related conditions

IBS Elements:
- Dysmotility
- Hypersensitivity
- Brain-gut interaction
- Immune dysregulation
- Dysbiosis
- Food intolerances
Diagnosis of Gluten Sensitivity

Gluten Sensitivity… … (NCGS)

• is not rare
• cannot be distinguished from celiac disease purely on a clinical basis
• can present with GI & with non-GI symptoms

Gluten free diet…
Can be tried AFTER celiac disease and wheat allergy have been excluded.

The Fad Factor of the Gluten Free Diet
ALL YOU CAN'T EAT BUFFET

Soy, Lactose, Gluten, Nuts, MSG
Non-celiac Gluten Sensitivity: The new kid that’s taking over the block?

Pros for GFD:
More awareness. Easier access. Lower costs?

Cons for GFD:
Inconsistencies regarding strictness

“T'have no idea what gluten is, either, but I'm avoiding it, just to be safe.”
Adopting a gluten-free diet is increasingly popular

2004 - 2014: GF products grew by >20% each year
2015: predicted $1.68 billion in the US

Celiac disease Seroprevalence in US ~1% (>2 million)

On Gluten Free Diet in the US >2 million

Diagnosed with celiac disease, & on a gluten free diet ~300,000 (i.e. ~15% of those with celiac disease)

<table>
<thead>
<tr>
<th>Finding</th>
<th>Untreated CeD</th>
<th>Treated CeD (on GFD)</th>
<th>NCGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms after gluten ingestion</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Specific CeD antibodies</td>
<td>Yes</td>
<td>No (often)</td>
<td>No</td>
</tr>
<tr>
<td>Villous atrophy (biopsy changes)</td>
<td>Yes</td>
<td>No (often)</td>
<td>No</td>
</tr>
<tr>
<td>Celiac genes (HLA DQ2/8)</td>
<td>Yes</td>
<td>Yes</td>
<td>No in ~40%</td>
</tr>
</tbody>
</table>

ACG Clinical Guidelines. Am J Gastroenterol. 2013
38 year old woman, comes to her doctor’s visit accompanied by her 2 young children

Longstanding abdominal bloating discomfort, episodic diarrhea & fatigue

Irritable bowel syndrome diagnosed 6 years previously

But minimal improvement in her symptoms with probiotics or with prescription medication
Case History II

- Started a gluten free diet (GFD) 8 months ago based on the suggestion of a worker at a health-food store
- Her symptoms are improved (by ~75%) but not resolved on the GFD
Case History II

Her questions:

- *Do I have celiac disease?*
- *Should my children be tested for celiac disease?*
- *Why are my celiac disease symptoms still persisting despite the GFD?*
### Celiac disease versus NCGS – Important differences

#### Celiac disease
- Gluten in diet causes:
  - Symptoms
  - Intestinal injury
  - High celiac antibodies
  - Malabsorption &
  - Nutritional deficiencies
  - Complications
    - Osteoporosis, malignancy
- Genetic predisposition
- Associated with other autoimmune disorders
- Requires lifelong, strict GFD

#### NCGS
- Gluten in diet causes:
  - Symptoms
- No known genetic predisposition
- No known complications
- Strictness & duration of GFD may vary

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Celiac Genetic Testing

<table>
<thead>
<tr>
<th></th>
<th>Celiac</th>
<th>General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>DQ2 Positive</td>
<td>79%</td>
<td>30%</td>
</tr>
<tr>
<td>DQ8 positive</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>DQ2 &amp; DQ8 +</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>DQ2 &amp; DQ8 Negative</td>
<td>&lt;1%</td>
<td>62%</td>
</tr>
</tbody>
</table>

- **Sensitivity:** ~100%;  
- **Specificity:** 31%  
- **NPV:** ~100%;  
- **PPV:** 1.5%

*Excellent at excluding celiac disease but cannot diagnose it!*

How to test:
- PCR of DNA extracted from cells in a cheek swab or blood sample

How often to test: Once in a lifetime

Who to test:
- Patients on a gluten-free diet without prior testing to attempt to exclude CeD
- Close relatives of patients with confirmed CeD wishing to know if they are at risk of developing CeD
- Hard to interpret / equivocal biopsy and / or antibody findings
## Factors in the differential diagnosis of Celiac disease *versus* NCGS

A clinical study of 226 patients on GFD without diagnosis:

<table>
<thead>
<tr>
<th>Clinical study of 226 patients on GFD without diagnosis</th>
<th>Celiac (n=101)</th>
<th>NCGS (n=125)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (y)</td>
<td>42.2</td>
<td>38.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Female gender</td>
<td>76.2%</td>
<td>78.4%</td>
<td>0.8</td>
</tr>
<tr>
<td>Typical CD symptoms (Diarrhea, weight loss)</td>
<td>67.3%</td>
<td>24.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history of celiac dis.</td>
<td>28.7%</td>
<td>12.8%</td>
<td>0.004</td>
</tr>
<tr>
<td>Other autoimmune disease</td>
<td>28.7%</td>
<td>12%</td>
<td>0.002</td>
</tr>
<tr>
<td>Any nutrient deficiency *</td>
<td>57.4%</td>
<td>18.4%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HLA DQ2 &amp; DQ8 NEGATIVE</td>
<td>&lt;1%</td>
<td>40%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Iron deficiency anemia, severe vitamin D deficiency, vitamin B12 or Zinc deficiency

Celiac Disease or NCGS? Prior celiac serology results (before GFD) very valuable

- Positive likelihood ratio for Celiac disease of a positive IgA tTG or IgA/IgG DGP (>2x ULN) at any time plus a clinical response to GFD was 130 (CI: 18.5-918.3).

- Positive likelihood ratio for NCGS of a negative IgA tTG or IgA/IgG DGP on a regular diet plus gluten responsive symptoms was 9.6 (CI: 5.5-16.9).

Seek out “old” celiac antibody serology results (prior to GFD)

Do I have celiac disease (or NCGS)?
Already on a GFD but no formal diagnosis

Gluten free diet holiday:
Consider Gluten challenge if:
- Antibody tests prior to GFD not available
- Antibody tests are now negative on GFD
- HLA testing positive for celiac-associated DQ2 or DQ8

- Why bother (if already following a GFD?)?
  - Certainty re diagnosis
    Celiac disease versus non-celiac gluten sensitivity
  - Certainty re need for lifelong, strict GFD
  - Certainty re potential for celiac complications & associations
  - Certainty re family risk (& need for high-risk screening)

Villous height versus crypt depth ratio

Normal Vh:Cd
2.5 to 3.5

Untreated Celiac Vh:Cd
<1.0 to 2.0

Villus height versus Crypt depth
Villous height falls on gluten exposure - but 3 g/day = 10 g/day
Gluten challenge in celiac disease

2013 American College of Gastroenterology - Guidelines on Celiac disease diagnosis & management

Key points

1. Genetic test before challenge – if negative no challenge needed (~40%)
2. Lower dose of gluten 3g versus 10-15g (1 slice of bread ~ 2.5 g)
3. Option for 2 week dropout (~90% sensitivity)
4. Delayed serology increases sensitivity

Summary of Gluten Sensitivity Disorders

• Celiac disease is common (~1% overall) and is increasing in prevalence

• Increased reporting of NCGS; true prevalence unknown

• Gluten-free diet is the mainstay of therapy for both conditions

• Differentiating CD from NCGS useful for longterm management and family risk assessment

• Tools to differentiate CD from NCGS
  1. Celiac serology (ideally prior to GFD)
  2. Genetic testing for celiac-associated HLA DQ2 or D8
  3. Gluten challenge with biopsy
Her questions:

• Do I have celiac disease?
  o Celiac disease in a cousin.
  o Iron deficiency at presentation
  o Celiac antibody tests not diagnostic
  o Gene testing not diagnostic (HLA DQ2 positive)
  o **GLUTEN CHALLENGE**: Led to villous atrophy and increase in celiac antibodies

• Answer **YES** – celiac disease confirmed
Case History II

Her questions:

- *Do I have celiac disease?* - **YES**
- *Should my children be tested for celiac disease?* - **YES**
Her questions:

• Why are my celiac disease symptoms still happening despite the GFD?
  ○ Occurs in at least 15% of celiac disease patients
  ○ Many reasons but the most common (~50%) is gluten exposure
Etiologies and Predictors of Diagnosis in Nonresponsive Celiac Disease

Other included:
Peptic ulcer disease (2),
Crohn’s disease (1),
Duodenal adenoma (1),
Food allergy (1),
Gastroparesis (1)

- Gluten Exposure 36%
- IBS 18%
- Other 8%
- Refractory Sprue 11%
- Small Intestinal Bacterial Overgrowth 6%
- Eating Disorder 6%
- Disaccharidase Deficiency 9%
- Microscopic Colitis 7%
"Before we come in, was any part of your home produced in a facility that also handles wheat, milk, nuts, eggs, or soy?"
70% of Celiac Disease Patients Report Gluten Exposures on GFD

- Intentional and known inadvertent lapses: 28%
- Intentional lapses but not known inadvertent lapses: 12%
- No intentional or known inadvertent lapses: 30%
- No intentional, some inadvertent lapses: 30%

Reported intentional and inadvertent gluten consumption (n=269)

How Much Gluten is Too Much?
Tiny gluten exposures perpetuate active disease

Histology post 90 day, 50 mg gluten/day microchallenge

Villus height: Crypt depth

Normal diet ~10,000 mg /day
Slice of bread ~2,000 mg
1/40th slice of bread ~50 mg

Healthy Control  |  Baseline  |  50 mg challenge

2.9  |  2.2  |  1.8

P = 0.03

Intestinal villi – seen three ways

Capsule Endoscopy

Dissecting microscope

Standard Histology

Normal intestine

Celiac disease