Gluten-Related Disorders in 2015

November 9, 2015

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THE UNIVERSITY OF CHICAGO MEDICINE
Celiac Disease Center
cureceliacdisease.org

THE UNIVERSITY OF CHICAGO MEDICINE
Comer Children’s Hospital
CELEBRATING 10 YEARS
Learning Objectives

- Distinguish between wheat allergy, celiac disease and non-celiac gluten sensitivity
- Analyze and define testing requirements to aid in the diagnosis of wheat allergy and gluten related disorders
- Advocate for accurate and timely diagnosis to improve patients quality of life
- Review literature to better understand the presentation of symptom, challenges of diagnosis and treatment options
"Gluten"-related disorders

- Wheat Allergy: ~0.1%
- Celiac Disease: 1%
- Gluten Sensitivity: ~0.5-1.0%

No gene associated

- IgE-mediated:
  - Infants and Bakers
    - HLA-DQ2, DQ8
    - Autoimmune disease
  - Any age
    - Likely Immune-mediated
    - Mostly adults

- Serum specific IgE
- CD autoantibodies
- Biopsy: No diagnostic marker
"Gluten"-related disorders

- Wheat Allergy
  - ~0.1%
  - No gene associated
  - Largely IgE-mediated
  - Children and Bakers

- Celiac Disease
  - 1%
  - HLA-DQ2, DQ8
  - Autoimmune disease
  - Any age

- Non-celiac Gluten Sensitivity
  - ?%
  - No gene associated
  - Immune-mediated?
  - Mostly adults

Symptoms:
- Respiratory, skin symptoms
- GI and extra-GI symptoms
“Gluten” - related disorders

- Wheat Allergy
  - ~0.1%
  - No gene associated
  - Largely IgE-mediated
  - Children and Bakers

- Celiac Disease
  - 1%
  - HLA-DQ2, DQ8
  - Autoimmune disease
  - Any age

- Non-celiac Gluten Sensitivity
  - ?%
  - No gene associated
  - Immune-mediated?
  - Mostly adults

Diagnostic markers:
- Serum specific IgE
- CD autoantibodies
- Biopsy
- No diagnostic marker
A hypersensitivity reaction to wheat proteins mediated through immune mechanisms and involving mast cell activation.

The immune response can be IgE mediated, non-IgE mediated, or both.

Most commonly a food allergy, but wheat can become a sensitizer when the exposure occurs through the skin or through the airways (Baker’s asthma)

Hill I, Fasano A, Guandalini S et al., Diagnosis and Treatment of Gluten Related Disorder. Manuscript submitted
Wheat Allergy

- IgE-mediated reactions to wheat albumin, globulin, α gliadin
- Some forms (e.g., EoE) may be IgE-mediated
- IgE-mediated reactions to ω-5 gliadin
- IgE-mediated reactions to ω-gliadin

- Respiratory Allergy
  - Asthma
- Food Allergy
  - GI manifestations
- WDEIA
- Contact Urticaria
  - Skin lesions
- Anaphylaxis
# Wheat Allergy in Children

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%) of patients; n = 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: male/female</td>
<td>32 (64)/18 (36)</td>
</tr>
<tr>
<td>Other atopic diseases*</td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>39 (78)</td>
</tr>
<tr>
<td>Asthma</td>
<td>24 (48)</td>
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<tr>
<td>Allergic rhinitis</td>
<td>17 (34)</td>
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<tr>
<td>Eosinophilic gastrointestinal disease*</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Eosinophilic oesophagitis</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Other food allergies*</td>
<td></td>
</tr>
<tr>
<td>Milk</td>
<td>40 (80)</td>
</tr>
<tr>
<td>White egg</td>
<td>36 (72)</td>
</tr>
<tr>
<td>Soy</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Fish</td>
<td>14 (28)</td>
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<tr>
<td>Peanut</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Tree nuts</td>
<td>13 (26)</td>
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<tr>
<td>Number of food allergens:*</td>
<td>Median 4; range: 3–7</td>
</tr>
<tr>
<td>3</td>
<td>4 (8)</td>
</tr>
<tr>
<td>4</td>
<td>33 (66)</td>
</tr>
<tr>
<td>≥5</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Family history of atopy</td>
<td>50 (100)</td>
</tr>
<tr>
<td>1 parents</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Both parents</td>
<td>41 (82)</td>
</tr>
<tr>
<td>Siblings</td>
<td>24 (62)</td>
</tr>
</tbody>
</table>

*throughout the whole observation period.
Clinical Manifestations of Wheat Allergy in Children

- alimentary tract and skin reactions
- only alimentary tract reactions
- only skin reactions
- bronchospasm
- anaphylaxis*
- vomiting
- loose stools
- abdominal pain
- urticaria, erythema
- eczema exacerbation

Czaja-Bulsa and Bulsa, Allergy, Asthma & Clinical Immunology 2014
Median Wheat IgE levels in patients with persistent or resolved wheat allergy

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Wheat specific IgE (kU/L)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outgrown</td>
<td>Persistent</td>
</tr>
<tr>
<td>0-2</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>2-4</td>
<td>10</td>
<td>27</td>
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<tr>
<td>4-6</td>
<td>7</td>
<td>49</td>
</tr>
<tr>
<td>6-8</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>8-10</td>
<td>6</td>
<td>42</td>
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<tr>
<td>10-12</td>
<td>5</td>
<td>36</td>
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<tr>
<td>12-14</td>
<td>4</td>
<td>35</td>
</tr>
<tr>
<td>14-16</td>
<td>4</td>
<td>33</td>
</tr>
<tr>
<td>16-18</td>
<td>4</td>
<td>30</td>
</tr>
</tbody>
</table>

*Mann-Whitney test.
Czaja-Bulsa and Bulsa, Allergy, Asthma & Clinical Immunology 2014
Relationship of peak wheat IgE level to persistence of wheat allergy during the first 18 years of life

Czaja-Bulsa and Bulsa, Allergy, Asthma & Clinical Immunology 2014
Gluten (or Wheat) related disorders

Wheat Allergy
~0.1%
No gene associated
Largely IgE-mediated
Children and Bakers

Celiac Disease
1%
HLA-DQ2, DQ8
Autoimmune disease
Any age

Non-celiac Gluten Sensitivity
?%
No gene associated
Immune-mediated?
Mostly adults

Serum specific IgE

CD autoantibodies
Biopsy

No diagnostic marker
Celiac Disease

- An immune-mediated systemic disorder elicited by gluten and related prolaminates in genetically susceptible individuals
- Characterized by a variable combination of:
  - Gluten-dependent clinical manifestations
  - CD-specific antibodies (autoantibodies against TG2, endomysial antibodies (EMA), and antibodies against deamidated forms of gliadin peptides (DGP)
  - HLA-DQ2 or HLA-DQ8 haplotypes; and
  - Enteropathy.

ESPGHAN Guidelines – Husby S et al., JPGN 2012
What Causes Celiac Disease?
The Genes

- **HLA-DQ2** (95% of celiacs)
- **HLA-DQ8** (5% of celiacs)

Note: You **must** have one of these genes to be celiac; But if you have them, you **may** or **may not** develop celiac
DQ2 or DQ8 Necessary but Not Sufficient

Caucasian populations

HLA-DQ2 or HLA-DQ8

Individuals with Celiac Disease
Rapidly Increasing Incidence of CD

Current prevalence in most Western Countries: 1%

West J et al., Am J Gastroenterol 2014
Antibiotics

Western Diet

Elimination of enteropathogens (H. pylori, Helmints)

Vaccines/reduced exposure to infections

C-sections /infant feeding (?)

Changes in microbiota “Dysbiosis”

*Celiac Disease
*Autoimmunity
*Food Allergies

Genetically susceptible individual

Feehley et al  *Seminars in Immunopathology* 2012
“Typical” Celiac Children
## Clinical Presentations

<table>
<thead>
<tr>
<th></th>
<th>Serology (tTG or EMA)</th>
<th>Symptoms</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic “Typical”</td>
<td>Positive</td>
<td>• Diarrhea</td>
<td>Marsh 2-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Abdominal Pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Distention</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anorexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Constipation</td>
<td></td>
</tr>
<tr>
<td>Symptomatic “Atypical”</td>
<td>Positive</td>
<td>Extra-intestinal</td>
<td>Marsh 1-3</td>
</tr>
<tr>
<td>Silent</td>
<td>Positive</td>
<td>None</td>
<td>Marsh 1-3</td>
</tr>
<tr>
<td>Potential</td>
<td>Positive</td>
<td>• None</td>
<td>Marsh 0-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Gastrointestinal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Extra-intestinal</td>
<td></td>
</tr>
</tbody>
</table>
Possible Presentations

• GI ("Typical") or Extra-GI ("Atypical")
• Silent
  – Positive antibodies
  – Intestinal damage at biopsy
  – *No symptoms*
• Potential
  – Positive antibodies
  – *No intestinal damage at biopsy*
  – ± Symptoms
Possible Presentations

- GI ("Typical") or Extra-GI ("Atypical")
- Silent
  - Positive antibodies
  - Intestinal damage at biopsy
  - *No symptoms*
- Potential
  - Positive antibodies
  - *No intestinal damage at biopsy*
  - ± Symptoms
The “Typical” (GI) Presentations

• Diarrhea
• Vomiting
• Failure to thrive or weight loss
• Abdominal bloating/pain
• Constipation
Main “Atypical”: Extra-Intestinal

- Malnutrition Related
  - Short stature
  - Delayed puberty
  - Iron-deficient anemia resistant to oral Fe
- Recurrent stomatitis
- Liver and biliary tract disease
  - Autoimmune Liver Disease
  - Benign hypertransaminasemia
- Skin disorders
  - Dermatitis Herpetiformis
  - Alopecia Areata
- Osteopenia/Osteoporosis
- Arthritis/Arthralgia
- Neurological problems
  - Headache
  - Peripheral Neuropathy
  - Seizures with occipital calcifications
  - Gluten Ataxia
- Behavioral changes & psychiatric disorders
  - Poor mood
  - Anxiety
  - Depression
- Women: sub-infertility
Main GI and Extra-GI manifestations

Atypical
- Fe-Deficient Anemia
- Osteopenia/Osteoporosis
- Arthritis
- Headaches
- Dental enamel defects
- Short stature

Typical
- Weight loss
- Abdominal Pain
- Anorexia
- Intussusception
- Diarrhea
- Failure to thrive
- Vomiting

6mo    5y    10y    15y    20y    >20
The Decline of “Typical” CeD

Gasbarrini GB et al., Intern Emerg Med 2014
Possible Presentations

- GI ("Typical") or Extra-GI ("Atypical")
- Silent
  - Positive antibodies
  - Intestinal damage at biopsy
  - *No symptoms*
- Potential
  - Positive antibodies
  - *No intestinal damage at biopsy*
  - ± Symptoms
Possible Presentations

• GI (‘‘Typical’’) or Extra-GI (‘‘Atypical’’)
• Silent
  – Positive antibodies
  – Intestinal damage at biopsy
  – *No symptoms*
• Potential
  – Positive antibodies
  – *No intestinal damage at biopsy*
  – ± Symptoms
Silent CeD: to treat or not to treat

**Autoantibodies**

**Health perception**

**Biopsy**

Kurppa K et al., Gastroenterology 2014
Silent CeD: to treat or not to treat

B

<table>
<thead>
<tr>
<th>Condition</th>
<th>Difference in mean changes in PGWB score (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>1.6 (0.4 to 2.8)</td>
<td>.025</td>
</tr>
<tr>
<td>Depression</td>
<td>0.3 (-0.5 to 1.2)</td>
<td>.281</td>
</tr>
<tr>
<td>Well-being</td>
<td>0.5 (-1.0 to 2.0)</td>
<td>.700</td>
</tr>
<tr>
<td>Self-control</td>
<td>0.3 (-0.7 to 1.4)</td>
<td>.775</td>
</tr>
<tr>
<td>General health</td>
<td>0.7 (-1.0 to 2.4)</td>
<td>.532</td>
</tr>
<tr>
<td>Vitality</td>
<td>0.4 (-1.5 to 2.2)</td>
<td>.670</td>
</tr>
</tbody>
</table>

Kurppa K et al., Gastroenterology 2014
Possible Presentations

• GI ("Typical") or Extra-GI ("Atypical")
• Silent
  – Positive antibodies
  – Intestinal damage at biopsy
  – *No symptoms*
• Potential
  – Positive antibodies
  – *No intestinal damage*
  – ± Symptoms

If left on gluten, almost 50% become full-blown celiacs in 3-5 years
Who Should be Tested?

• **Children and adolescents with otherwise unexplained GI symptoms and signs:**
  – Chronic or intermittent diarrhea
  – Nausea or vomiting
  – Chronic abdominal pain, cramping or distension
  – Chronic constipation
  – Failure to thrive, weight loss, stunted growth
  – Recurrent aphthous stomatitis

• **Children and adolescents with otherwise unexplained Extra-GI symptoms and signs:**
  – Short Stature; delayed puberty, amenorrhea
  – Iron-deficiency anemia, chronic fatigue
  – Dermatitis Herpetiformis–like rash
  – Fracture with inadequate traumas/osteopenia/osteoporosis
  – Abnormal liver biochemistry (elevated AST, ALT)
Who Should be Tested?

• Asymptomatic children and adolescents at increased risk for CD such as:
  • Type 1 diabetes mellitus (T1DM)
  • Autoimmune thyroid disease
  • Down syndrome
  • Turner syndrome
  • Williams syndrome
  • Selective immunoglobulin A (IgA) deficiency
  • Autoimmune liver disease
  • First-degree relatives with CD (overall prevalence 8.1%, varying from 13% in sisters, daughters to 3% in parents)
### Celiac-specific Antibodies: the Best Biomarkers

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA /IgA</td>
<td>31.8 (18.6-54.3)</td>
<td>0.067 (0.038-0.118)</td>
</tr>
<tr>
<td>Anti-TG2 /IgA</td>
<td>21.8 (12.9-36.8)</td>
<td>0.060 (0.040-0.090)</td>
</tr>
<tr>
<td>Anti-DGP /IgG</td>
<td>13.6 (8.1-22.8)</td>
<td>0.061 (0.017-0.221)</td>
</tr>
<tr>
<td>Anti-DGP /IgA</td>
<td>9.4 (6.8-13.1)</td>
<td>0.121 (0.072-0.203)</td>
</tr>
<tr>
<td>AGA /IgA</td>
<td>7.3 (4.5-11.8)</td>
<td>0.186 (0.095-0.362)</td>
</tr>
</tbody>
</table>

Giersiepen K et al., JPGN 2012
How to Test for Celiac Disease

- **Serum anti-Tissue Transglutaminase IgA (TTG)**
  - Sensitivity: **98%** (74-100%) - beware of IgA-deficient! (*)
  - Specificity: **97%** (78-100% - correlating with titers)
  - Beware of low titers: false positive often found in other conditions

- **Serum anti-Endomysium Antibodies IgA (EMA)**
  - Low to moderate sensitivity (around 85%)
  - **High specificity: 98.2%** (97-100%)

(*) IgA deficient is a subject who has less than 20 mg/dl of total serum IgA: TTG-IgG should be performed only in these cases

**Note:** There is a very good correlation between serum titers of TTG-IgA or EMA and tissue damage - Husby S et al., JPGN 2012
Why anti-EMA is Not the Best Initial Test to Screen for Celiac Disease?

- Requires technical expertise
- Observer-dependent
- Costly and ecologically unfriendly
Careful!

Other causes of elevated TTG-IgA

- Liver Disease
- Any Autoimmune Condition (esp. T1DM!)
- Crohn’s disease
- Tumors
- Viral Infections
Deamidated Gliadin Peptides (DGP)

• DGP: sensitivity and specificity in screening for celiac disease similar to TTG-IgA
• DGP-IgG: better sensitivity and specificity than DGP-IgA

• DGP more often positive than TTG-IgA in very young children (below age 2), making them the preferred screening test for this age group

All serological tests for CD depend for diagnostic reliability on the patient being on gluten! Testing for serology someone who has been for ≥6 weeks on a strict gluten-free diet (GFD) is a common mistake that must be avoided, as levels of antibodies begin to decline 2-3 weeks after beginning GFD, and if the titers were only moderately elevated to being with, they may well be completely normal after 6 weeks on a GFD!
Endoscopic Changes in Celiac Disease

Mosaic
Sparse folds
Scalloping
Nodularity

Pellegrino S et al., *Digestion* 2013
Mucosal damage is progressive: the Marsh scoring system

- Normal 0
- Infiltrative 1
- Hyperplastic 2
- Partial atrophy 3a
- Subtotal atrophy 3b
- Total atrophy 3c
Microscopic Enteritis (Marsh 1-2)

Rostami K et al., *World J Gastroenterol* 2015
## Causes of Microscopic Enteritis

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coeliac disease</td>
<td>[7-8]</td>
</tr>
<tr>
<td>Non coeliac gluten sensitivity</td>
<td>[52-53]</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>[15,57]</td>
</tr>
<tr>
<td>Other infections, parasites</td>
<td>[92]</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>[64]</td>
</tr>
<tr>
<td>Bacterial overgrowth</td>
<td>[58-60]</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>[13]</td>
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<tr>
<td>Eosinophilic gastroenteritis</td>
<td>[90]</td>
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<tr>
<td>Collagenous gastroenteritis</td>
<td>[1]</td>
</tr>
<tr>
<td>Microvillous inclusion disease</td>
<td>[12]</td>
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<tr>
<td>Autoimmune enteropathy</td>
<td>[68]</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
<td>[2,15,68]</td>
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<tr>
<td>Irritable bowel syndrome</td>
<td>[3,75]</td>
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<tr>
<td>Inflammatory bowel disease</td>
<td>[16]</td>
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<tr>
<td>Food allergy</td>
<td>[93]</td>
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<tr>
<td>Food intolerances</td>
<td>[76]</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>[94]</td>
</tr>
</tbody>
</table>

Rostami K et al., *World J Gastroenterol* 2015
Can we diagnose celiac disease without the histology?

The new ESPGHAN guidelines
Child or teenager suspect of CD

TTG-IgA >10x normal

EMA positive

EMA negative

CELIAC

TTG-IgA and total IgA normal

NOT CELIAC

TTG-IgA elevated but <10x normal

EGD

Marsh 0-1

POTENTIAL CELIAC

Marsh 1-3

FALSE POSITIVE

CELIAC

ESPGHAN diagnostic scheme
Decline of specific antibodies on the GFD

74% decrease after 3 months of diet

Hogen-Esch C. et al., Pediatrics 2011
### Follow-up of Celiac Patients

<table>
<thead>
<tr>
<th></th>
<th>At diagnosis</th>
<th>At 3-6 months</th>
<th>Every 1-2 years</th>
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<tbody>
<tr>
<td><strong>EMA</strong></td>
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<td><strong>TTG-IgA</strong></td>
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<td><strong>DGP-IgG</strong></td>
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<td><strong>CBC</strong></td>
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<tr>
<td><strong>Fe studies</strong></td>
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<tr>
<td><strong>TSH+T4</strong></td>
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<tr>
<td><strong>Vitamin D</strong></td>
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<tr>
<td><strong>Dietitian review</strong></td>
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<tr>
<td><strong>Cholesterol</strong></td>
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<tr>
<td><strong>BMD</strong></td>
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</tbody>
</table>

* + *Timely colon cancer screening*
Follow-up often Inadequate

What is 20 ppm?

- 0.002% gluten or 2 mg/100gm
- 20 mg gluten per 1 kg of food
- One minute in two years!

Study determined how much gluten may be tolerated

- 0, 10 or 50 mg gluten daily for 90 days

Conclusion:

- 50 mg or more of gluten induced villous damage

Healing of Intestine in Children

First biopsy

Repeat Biopsy

Ghazzawi Y at al., JPGN 2014
Healing of Intestine in Adults

Lanzini A et al., Alim Pharmacol Ther 2009
Only adults

Lebwohl B. et al., Aliment Pharmacol Ther 2014
Adults and Children
Adherence to GFD in adults

Leffler D et al., Am J Gastro 2015
"Gluten" - related disorders

- Wheat Allergy
  - ~0.1%
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Diagnostic markers:
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- CD autoantibodies
- Biopsy
- No diagnostic marker
Biesekierski JR et al., Gastroenterology 2013
Effect of FODMAP withdrawal

No effect of gluten

Biesekierski JR et al
Gastroenterology 2013
Number of studies so far published on NCGS that utilized pure gluten (not wheat) to challenge: 0 (Zero)

"Of note, no study on NCGS has specifically used as the re-challenging agent gluten or gliadin" – Molina-Infante J et al., Aliment Pharmacol Ther April 2015
The "GLUTOX" Trial: A Randomized, Double Blind, Placebo Controlled Crossover Study on "Non-Celiac Gluten Sensitivity"

100 patients with IBS-like symptoms, no celiac or wheat allergy

81 patients improved
19 patients did not improve

NCGS excluded
56 patients (75%) did not react

GFD for 3 wks

Gluten challenge
25 patients (25%) reacted

NCGS confirmed

Elli L et al., DDW 2015
The only published study testing the effect of gluten in NCGS

Di Sabatino A. et al., Clin Gastroenterol Hepatol, 2015
Nonceliac Gluten Sensitivity or Wheat Intolerance Syndrome?

Stefano Guandalini, MD¹, and Isabel Polanco, MD²

The increase in world-wide consumption of a Mediterranean diet, which includes a wide range of wheat-based foods, has possibly contributed to an alarming rise in the incidence of wheat (gluten?)-related disorders.¹² Gluten, the main protein complex in wheat, barley, and rye, is a mixture of alcohol-insoluble ("glutenins") and alcohol-soluble ("gliadins") proteins.³ Gliadins are a group of proline and glutamine-rich proteins resistant to digestion in the gastrointestinal tract.

Gluten consumption has been linked to a wide range of systemic manifestations were most commonly tiredness, headache, fibromyalgia-like joint/muscle pain, leg or arm numbness, "foggy mind," dermatitis or skin rash, depression, anxiety, and anemia. Of note, in this study, 95% of patients reported the appearance of symptoms every time or often after the ingestion of gluten-containing food. In more than one-half of these patients, the symptoms occurred within 6 hours after gluten ingestion; in about 40%, between 6 and 24 hours after ingestion; and only in less than 10%, more than 24 hours after ingestion. Similar data had been published
NCGS

WHEAT INTOLEANCE SYNDROME

Guandalini S and Polanco I, J Pediatr 2015
The umbrella of Wheat Intolerance Syndrome:

- Gluten sensitive
- ATI sensitive
- FODMAP sensitive
- Early-stage celiac
- Non IgE-wheat allergic
- Placebo/Nocebo
WIS – A Practical Approach

Pt on GFD

Willing to undergo gluten challenge
- Gluten for ≥6 weeks
  - TTG and Biopsy
    - Positive: Celiac
    - Negative: No Celiac

Unwilling to abandon the GFD
- HLA-DQ2, DQ8
  - Positive
    - Enjoy your GFD: *But remember you could be celiac*
  - Negative: No Celiac: Enjoy your GFD!

Symptoms recurred?
- Yes: WIS
- No: WIS ruled out
In conclusion

- **Wheat Allergy**
  - More common in children
  - Mostly IgE-mediated

- **Celiac disease:**
  - Fast increasing prevalence
  - Changing patterns of presentations
  - Celiac serology needed for diagnosis and follow-up
  - GFD more effective in children than in adults

- **NCGS (or better “Wheat Intolerance Syndrome”)**
  - No diagnostic marker available
  - Likely a mixture of various conditions