The Changing Face of Celiac Disease

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Special Thanks

Blair and Steve Raber, founders of the Children’s National Celiac Disease Program

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Learning Objectives

At the end of the talk, the participants will:

1. Understand the basics of the epidemiology and pathophysiology of celiac disease
2. Know the recommended approach to diagnosing CD
3. Appreciate the need for greater awareness about the varied presentations of CD
Overview

Brief Background on the Basics of CD

1. Definition and Epidemiology
2. Autoimmune Nature and Impact
3. How to Diagnose CD in 2016
   - Distinguish CD from Non-Celiac Gluten Sensitivity
4. Clinical Presentations
Permanent intolerance to gliadin

*a protein in wheat, barley and rye*

Genetic predisposition

Injury is immunologically mediated
Epidemiology: Global Disease

CD affects ~ 1% of most of world

Most cases are not diagnosed

Suffer from symptoms
Exposed to risk of complications

Increased awareness and case finding is needed
Epidemiology: Current Data

Prevalence in U.S.: 1:133 (sero screening)

Children at Increased Risk
- Type 1 diabetes mellitus: 5-10%
- Down syndrome: 5-10%
- Thyroid disease: 5-10%
- IgA deficiency: 2-3%

Results similar to those in Europe
Autoimmune Pathogenesis
Gliadin protein taken up by the intestine

HLA-DQ2 binds gliadin – starts the autoimmune process

Facilitates connection of antigen presenting cell to helper T cell - considered to be the central event

This connection starts the immune cascade -> specific antibodies + cell signaling proteins (cytokines)
Current Understanding

Strong specific HLA association overlaps with other autoimmune diseases

Alteration in immune response can lead to injury to other targets

An altered immune response may be caused by:

- differences in the genes
- sequence of events that trigger inflammation
Changing Face of Diagnosis
### Initial Serology: Which Test?

<table>
<thead>
<tr>
<th>Ab Tests (all IgA)</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliadin</td>
<td>70%</td>
<td>75%</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Deamidated Gliadin</td>
<td>90%</td>
<td>91%</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>Endomysial</td>
<td>90%</td>
<td>98%</td>
<td>95%</td>
<td>85%</td>
</tr>
<tr>
<td>tTG human</td>
<td>95%</td>
<td>99%</td>
<td>99%</td>
<td>95%</td>
</tr>
</tbody>
</table>

*Adapted from Fasano  NEJM 2012*
Initial Serology

Quantitative IgA

IgA antibodies:

anti-tissue transglutaminase (tTG)

(anti-endomysial - used in special situations, e.g. children with autoimmune dis)

Highest positive predictive value >95%
Serology: Limitations

False positive and negative values occur esp with autoimmune disease

Antibody levels can fall slowly after healing

IgA deficiency is associated with CD

Ab levels are less accurate if age < 2yr
Correlation of Ab levels and inflammation is not perfect

Many adult groups are now routinely doing follow-up EGD 1 yr into a gluten-free diet

Preliminary studies in children raise similar concerns

No routine f/u EGD in children yet but threshold is low to repeat in poor responders
Is There a Genetic Test?

**HLA testing**

Almost all CD patients are DQ2 and/or DQ8 positive
But so is ~35% of population
‘Positive’ test has little meaning
Expensive - insurance does not always cover test

**Value of negative HLA testing**

High negative predictive value
If DQ2/DQ8 negative, only ~ 2 % chance of CD
New ESPGHAN Proposal for Dx

Initial cut-off:
10x or greater increase in IgA anti-tTG symptomatic (listed 16 possibilities)

Their protocol calls for additional testing:
IgA anti-endomysial Ab
HLA DQ2 and DQ8 testing

If all tests are positive -> diagnosis ‘confirmed’
No endoscopy + biopsy would be done
Diagnosis by Serology?

Proposal not yet widely accepted

Validity in large populations still under study

- Lack of standardization of assays
- Positive predictive value not clearly established
- False positive patients reported

Not yet endorsed by NASPGHAN
Diagnosis of CD in US, 2016

Quantitative IgA

IgA antibodies:

- anti-tissue transglutaminase (tTG)
- anti-endomysial (used in special situations, e.g. children with autoimmune dis)

Positive serology -> endoscopy + biopsy
What Is Non-Celiac Gluten Sensitivity?

Reaction to gluten - wide range of symptoms

Requires testing – negative/normal results

Serologic testing for CD (tTG and/or EMA)
Endoscopy: intestinal histology
Immuno-allergy tests to wheat

Resolution of symptoms on a gluten-free diet

Clinical Manifestations
Clinical Manifestation

‘Classic’ CD: onset in 1st 2 years of life
poor growth, diarrhea, abd distention
Clinical Manifestations

‘Classic’
Later Onset GI
Non-GI Conditions
Asymptomatic
Clinical Manifestation

“GI” CD

Atypical CD
Could This Be Celiac Disease?

<table>
<thead>
<tr>
<th>Associated Autoimmune Diseases</th>
<th>Behavioral/Psychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Type 1 Diabetes (insulin dependent) * Hypothyroidism * Hyperthyroidism (Grave’s Disease) * Secondary Hyperparathyroidism * Sjogren’s Syndrome * Addison’s Disease * Dilated (congestive) cardiomyopathy ?? * Alopecia Areata – patchy hair loss * Rheumatoid Arthritis * Fibromyalgia * Collagen-Vascular Disease * Multiple Sclerosis * Systemic Lupus Erythematosus * Reynaud’s Syndrome</td>
<td>* Depression * Attention Deficit Disorder (ADD)/AD Hyperactivity Disorder (ADHD)/Autism * Hypochondria * Inability to concentrate, “brain fog” * Anxiety * Neurosis * Moodiness * Obsessive-Compulsive Disorder</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Dermatologic and Mucous Membranes</th>
<th>Gastrointestinal</th>
</tr>
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<table>
<thead>
<tr>
<th>Hematologic</th>
<th>Nutritional</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Anemia * Leukopenia (low white blood count) * Thrombocytopenia (low platelet count) * Thrombocytosis (increased platelet count) * Bruising * Vitamin K deficiency * Bleeding</td>
<td>* Weight loss * Stunted growth * Poor weight gain (“failure to thrive”) * Low blood sugar</td>
</tr>
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<table>
<thead>
<tr>
<th>Neurological</th>
<th>Renal</th>
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<tbody>
<tr>
<td>* Peripheral Neuropathies * Paraplegia * Ataxia – balance disturbance * Seizures * Migraines/headaches * Brain Atrophy and Dementia</td>
<td>* IgA Nephropathy</td>
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<thead>
<tr>
<th>Reproductive</th>
<th>Skeletal</th>
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</thead>
<tbody>
<tr>
<td>* Premature menopause * Infertility * Abnormal menstrual cycles * Spontaneous miscarriage * Delayed puberty</td>
<td>* Osteoporosis/Osteopenia * Joint, bone, muscle pain * Dental enamel defects * Clubbing</td>
</tr>
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<thead>
<tr>
<th>Respiratory</th>
<th>Other Symptoms</th>
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</thead>
<tbody>
<tr>
<td>* Respiratory problems * Asthma</td>
<td>* Edema * Tetany – spasms of hands * Fatigue, Chronic Fatigue Syndrome * Swelling and inflammation, chronic infections * Night blindness</td>
</tr>
</tbody>
</table>
Behavioral/Psychiatric

Anxiety
Depression
Moodiness
Neurosis
Processing Disorders

Attention Deficit Disorder
Hypochondria
Inability to Concentrate
Obsessive-compulsive

(Autism Spectrum Disorder)
Remember

CD affects much more than the GI tract

CD can be associated with every organ system

Must think of CD to screen for it

any patient with hard-to-explain findings

patients with psychological or psychiatric problems

Screen for celiac disease before trying GF diet
Conclusions

Changing face of epidemiology and pathogenesis
Only about 20% of patients have been diagnosed
Autoimmune nature helps explain wide range of presentations

Changing face of diagnosis
Serology holds promise but requires further fine-tuning
Endoscopy still considered ‘gold standard’ in US/Canada

Changing face of clinical presentation
Have a low threshold to test, esp in patients with psychological and psychiatric disease
### CD, Gluten Sensitivity, Wheat Allergy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Celiac Dis</th>
<th>Glut Sens</th>
<th>Wheat Aller</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time: exposure to symptoms</td>
<td>wks to yrs</td>
<td>hrs to days</td>
<td>min to hr</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Autoimmune innate + adapt</td>
<td>Possible innate</td>
<td>Allergic immune resp</td>
</tr>
<tr>
<td>HLA antigen</td>
<td>Most are DQ2 or DQ8 pos</td>
<td>No role</td>
<td>No role</td>
</tr>
<tr>
<td>Enteropathy</td>
<td>Almost always</td>
<td>Never</td>
<td>Never (eos)</td>
</tr>
</tbody>
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