Learning Objectives

At the end of this presentation the participant will be able to:
1) Recognize the different presentations of celiac disease
2) Understand current serologic screening strategies
3) Risk groups and management of celiac disease

Celiac Disease History

- CD was first described by the ancient Greek physician Aretaeus of Cappadocia
- Because of the prominence of GI symptoms that characterized the disorder, he named it koeliac from the Greek word “abdominal”

Three Breakthrough Discoveries

- 1950-Willem Dicke makes the connection between certain cereals and the disease
- 1970- HLA-DQ2 associated with celiac disease and dermatitis herpetiformis
- 1997- Dr. Schuppan identifies the role of tissue transglutaminase (TTG) in celiac disease
Terminology

- **Wheat allergy**
  - An abnormal immunologic reaction involving IgE antibodies to one or more proteins found in wheat

- **Gluten Intolerance**
  - Functional symptoms related to gluten exposure without an immune response

What is Celiac Disease?

- Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains including wheat, rye, and barley in genetically susceptible individuals

- Contrary to common belief, gluten enteropathy is a systemic disease rather than merely an ailment of the alimentary tract

Epidemiology

- CD is one of the most common lifelong disorders
  - Affects 0.6 to 1% of the population worldwide
  - Prevalence of the disease has increased in the past few decades

Pathogenesis

- Multifactorial, but still poorly understood

What is Gluten?

- Is the protein from wheat, rye, and barley
- Is required to trigger the immune response in celiac disease
- Is not directly toxic to intestinal mucosa per se, but rather toxicity requires the participation of an endogenous effector
Environmental Factors

- Breast feeding
- Infant diet
- Intestinal infections
- Intestinal microbiome

Is the Incidence Modifiable?

- Risk of Celiac Disease Autoimmunity and Timing of Gluten Introduction in the Diet of Infants at Increased Risk of Disease

Genetic Factors

- Genetic background plays a key role
  - HLA class II genes: DQ2 and DQ8 are prerequisite genetic factors for the development of celiac disease
- In Celiac disease
  - HLA-DQ2 (90%)
  - HLA-DQ8 (5%)
What is the Role of Tissue Transglutaminase (TTG-2)

- An enzyme in the intestine that modifies gluten antigens, thus increasing their immunogenicity
- This critical process is termed deamidation and is required for the binding of gluten peptides to HLA-DQ2 and HLA-DQ8 molecules on APC
- The autoantibodies directed to TTG do not appear to play a pathogenic role in enteropathy

Clinical Presentation

- Clinical manifestations are highly variable
  - May present at any age
  - Involve multiple organ systems

Clinical Spectrum Divided in 4 Categories

1) CD with Classic Symptoms
2) CD with Extra-intestinal Manifestations
3) Silent CD
4) Latent CD

CD with Classic Symptoms

- Characterized by GI symptoms starting between 6 and 24 mo of age, after the introduction of gluten in the diet
  - Impaired growth
  - Chronic diarrhea
  - Abdominal distention
  - Muscle wasting
  - FTT
  - Unhappy behavior

- "Classic" triad: malabsorption, diarrhea, and FTT
- This presentation is now recognized to be the exception, rather than the rule
CD with Nonclassic Symptoms
- Observed in older children
- Unusual intestinal complaints
  - recurrent abdominal pain, vomiting, constipation
- Extra-intestinal manifestations that can affect multiple organs
- Now believed to account for >50% of documented cases of CD

CD involves multiple organ systems

Iron Deficiency Anemia
- Most frequent extra-intestinal manifestation experienced by CD patients
- Refractory to iron therapy due to villous atrophy and poor iron absorption in the proximal duodenum
- Responds to GFD

Dermatitis Herpetiformis
- Strong association with latent or silent forms of CD
- Recognized as pathognomonic of CD
- Responds to GFD

Hepatic Manifestations
- Elevated liver enzymes
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Elevated liver enzymes
- May be the only manifestation of CD
- As many as 9% of patients with elevated transaminase levels of unclear etiology may have silent CD
- Liver enzymes normalize on a GFD
### Osteoporosis
- Attributed to calcium and Vitamin D malabsorption
- May present with recurrent fractures in young adults with CD
- Prompt introduction of a GFD can lead to a complete recovery of the bone density

### Reproductive Manifestations
- Infertility
- Increased rate of spontaneous abortions
  - 8.9 X RR vs healthy subjects
- Increased frequency of low birth weight infants

### Short stature and delayed puberty
- Short stature may be the only manifestation of CD
- As many as 8-10% of children with “idiopathic short stature” may have CD on serologic testing
- Adolescent females with untreated CD may have delayed onset of menarche

### Diagnosis
- The most important diagnostic test in CD is the **suspicion of the disease**
- Serology is used to screen for CD
- The gold standard of CD diagnosis is a small intestinal biopsy showing the typical celiac enteropathy

### CD Histology
- Villous atrophy
- Crypt hyperplasia
- Intraepithelial lymphocytosis

### Serology
- The most sensitive serologic tests are based on the use of IgA isotypes
- Available tests include:
  - Antigliadin antibodies (AGA)
  - Endomysial antibodies (EMA)
  - Tissue transglutaminase antibodies (TTG)
  - Anti-DGP antibodies (Anti-DGP)
Antigliadin Antibodies (AGA)

- AGAs have been widely used since early 80’s
- Test for both IgA-AGA and IgG-AGA
  - Sensitivity: 80%
  - Specificity: 80-90%
- Conventional gliadin antibody testing is no longer recommended for identifying individuals with CD due to variable and inferior accuracy

IgA Endomysial Antibody (EMA)

- Based on immunofluorescent staining technique
- Sensitivity: >90%
- Specificity: >95%
- However IgA EMA is more expensive, operator dependent, and time consuming

IgA TTG Antibodies

- Is less costly because utilizes an ELISA technique
- Sensitivity: 92-100%
- Specificity: 91-100%
- TTG essay is the universally recommended screening test for CD

Anti-deamidated gliadin peptide antibodies (IgA-anti DGP)

- Might be among the first antibodies to appear in the sera of subjects who later develop celiac disease
- Sensitivity: 79% when used as single test
- Sensitivity: 93% when combined EMA and anti-DGP
- Suggested as a promising new method of identifying early-stage celiac disease

HLA testing for HLA-DQ2 and HLA-DQ8

- Should be performed in patients where the diagnosis of celiac disease is in question (example - all antibody testing negative but severe symptoms)
- Equivocal biopsy results with + serologies
- 1st degree relative of an index case
- Testing only helpful if is NEGATIVE

Why should we get an IgA Level?

- Selective IgA deficiency occurs more commonly in patients with CD than in the general population
- Prevalence is 2-3% in patients with CD
- Appropriate evaluation of CD includes ruling out total IgA deficiency to minimize false negative serologic results
Biopsy Confirmation Remains Necessary

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
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</thead>
<tbody>
<tr>
<td>IgA AGA</td>
<td>85 (37-100)</td>
<td>90 (47-94)</td>
<td>18</td>
<td>99</td>
</tr>
<tr>
<td>IgG AGA</td>
<td>85 (42-100)</td>
<td>80 (30-94)</td>
<td>31</td>
<td>99</td>
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<tr>
<td>EMA</td>
<td>95 (86-100)</td>
<td>99 (97-100)</td>
<td>83</td>
<td>99</td>
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<tr>
<td>IgA TTG</td>
<td>98 (78-100)</td>
<td>98 (90-100)</td>
<td>72</td>
<td>99</td>
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<tr>
<td>IgG TTG</td>
<td>70 (45-95)</td>
<td>95 (94-100)</td>
<td>42</td>
<td>99</td>
</tr>
<tr>
<td>IgA anti-DGP</td>
<td>88 (74-100)</td>
<td>95 (90-99)</td>
<td>44</td>
<td>99</td>
</tr>
</tbody>
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Leffler, Schuppan AJG 2010

Who Should be Screened for CD?

- The best approach is an active case-finding strategy

  1. Children with persistent gastrointestinal symptoms
  2. Children with extra-intestinal symptoms of CD
  3. Asymptomatic children who belong to high risk groups

High-Risk groups for celiac disease

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relative of CD patient</td>
<td>10-15%</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td>3-12%</td>
</tr>
<tr>
<td>Williams Syndrome</td>
<td>8%</td>
</tr>
<tr>
<td>Turner Syndrome</td>
<td>4-8%</td>
</tr>
<tr>
<td>Down Syndrome</td>
<td>5%</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>5%</td>
</tr>
<tr>
<td>Secretory IgA deficiency</td>
<td>2-3%</td>
</tr>
<tr>
<td>General Population</td>
<td>1%</td>
</tr>
</tbody>
</table>

How do we screen?

- Obtain IgA TTG and a total IgA level in any suspicious or high risk patient

- Antibodies against DGP may be used as additional tests in patients who are negative for other CD-specific antibodies but in whom clinical symptoms raise a strong suspicion of CD

  * Celiac panels, such as testing for antibodies to TTG, anti-gliadin, and endomysium do not add value over single tests

Prometheus Celiac Disease Testing

- Celiac Serology (TTG, EMA, DGP, total IgA) $290
- Celiac Genetics (HLA DQ2/DQ8 risk stratification) $510
- Celiac Plus (includes both antibodies + genetic tests) $800
- TTG IgA $8.60

What to do with a Type 1 DM patient

- The dx of DM precedes that of celiac disease by years
- Should we screen for CD in this population? Yes
- Should an asymptomatic diabetic be on GFD? Decision might be controversial if this is picked up on screening
- GFD improves glycemic control and GI symptoms
- GFD improves osteopenia, infertility, malignancy
Management

- Treatment is recommdned for symptomatic and asymptomatic children with confirmed dx of CD
- The gluten-free diet (GFD) is the “drug of choice”
  - Implies excluding wheat, rye, and barley for life
- Should be started ONLY after the dx has been confirmed by intestinal biopsy

The Gluten-Free Diet

- GFD is complex and can easily overwhelm patients as it has both lifestyle and financial implications
- It is a challenge to children and families
- Adolescents have a hard time, with reported compliance between 50-80%
- Physician should stress the advantages with regard to the prevention of complications of CD
  - Malignancy (EATL), osteoporosis, anemia, improvement in fertility and birth outcomes

Hidden gluten is a problem

- Milk, butter, and cheese
- Fresh, frozen, or canned fruits and vegetables
- Fresh meats, fish, poultry, eggs
- Beans and nuts
- Corn and rice

What is gluten-free?

- Milk, butter, and cheese
- Fresh, frozen, or canned fruits and vegetables
- Fresh meats, fish, poultry, eggs
- Beans and nuts
- Corn and rice

Which problems do families face?

- Increased $ of food
- Inadequate food labeling
- Lack of information while eating at restaurants
- Use of gluten-containing products in medications
- Conflicting information regarding the GFD
Dietary concerns with the GFD

- Enrichment/Fortification
  - Most GF cereals, pasta and bread are not fortified
  - Low on iron, folate, B vitamins

- Weight gain on GFD
  - Excessive reliance of protein-rich, high fat foods

- Low fiber content
  - Induces constipation or exacerbates IBS symptoms

Key Elements in Management of CD

- Consultation with a skilled dietician
- Education about the disease
- Lifelong adherence to a gluten-free diet
- Identification and treatment of nutritional deficiencies
- Access to an advocacy group
- Continuous long-term follow up by a multidisciplinary team

Associations

- Most countries have national support groups easily found on the internet
- These groups provide emotional and social assistance
- The Celiac Disease Foundation is an excellent resource for patients (www.celiac.org)
- Provides dietary instructions and gluten-free recipes

Take Home Points

- CD is a common, but frequently unrecognized disease
- Increased awareness of the extra-intestinal manifestations, coupled with a low threshold for serological testing will help uncover a large proportion of the submerged iceberg
- Primary care practice provides the best opportunity to identify individuals who are at risk for CD and need referral for definitive diagnosis

Take Home Points

- Increased LFTs and FTT, think celiac disease
- Persistent iron deficiency anemia despite therapy needs a TTG screen
- CD with classic symptoms is now the exception rather than the rule
Celiac Disease is out there

Look for it!

Bibliography

- Rewers M. Epidemiology of Celiac Disease: What are the prevalence, incidence, and progression of celiac disease? Gastroenterology 2005; 128(4):S47-S51