Celiac Disease Update

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Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.
What Is Celiac Disease?

- Celiac disease is a unique autoimmune disorder triggered by gluten.
- Originally considered a rare malabsorption syndrome of childhood.
- Now recognized as a common condition that may be diagnosed at any age and that affects many organ systems.
- This presentation discusses the pathogenesis, diagnosis, and management of the disease.

Pathogenesis

- **The Role of Gluten**
  - Celiac disease is induced by the ingestion of gluten—the entire protein component of wheat the gliadin fraction of gluten contains the bulk of the toxic components.

- **Mucosal Immune Responses**
  - Immune responses to gliadin fractions promote an inflammatory reaction primarily in the upper small intestine.

- **Genetic Factors**
  - Requires the alleles that encode for HLA-DQ2 or HLA-DQ8

- **Environmental Factors**
  - Protective effect of breast-feeding
  - Introduction of gluten < age 4
Gluten

- The gluten protein is poorly absorbed in the upper GI tract. The gliadin component is toxic.

- Gluten is derived from wheat, barley and rye.

- Gliadin fraction is resistant to degradation by gastric, pancreatic and intestinal brush-boarder proteases in the intestine.

Interaction of Gluten with Environmental, Immune, and Genetic Factors in Celiac Disease
Genetic Factors

- Genetic background plays a key role in disposition to the disease.
- 90% of patients express the HLA-DQ2 haplotype compared to one third of the general population.
- 5% express the HLA-DQ8 haplotype.
- These genes are necessary for the development of celiac disease.
- There is a 10% prevalence among first degree relatives.
Environmental Factors

• Play an important role in development of celiac disease.

• Breast feeding is protective.

• Introduction of gluten before age 4 increases the risk.

• Marginal risk after age 7 months.

• Certain infections increase the risk
  • Rotavirus
Epidemiology

- Rate in adults and children 1% of the population.
  - Regional differences 0.3% in Germany, 2.4% in Finland.

- Rates are increasing in many developing countries because of westernization of the diet.
  - China, India
Clinical Manifestations

- Vary Greatly according to age.
  - Children-
    - Generally diarrhea, abdominal distention, failure to thrive, but constipation, vomiting, irritability and anorexia are common.
  - Older children and adolescents-
    - Extraintestinal manifestations-short stature neurologic symptoms or anemia.
Clinical Manifestations

- Adults
  - Two to three times more likely in women.
  - Autoimmune diseases more common in women.
  - Osteoporosis and iron deficiency diagnosed more often in women.
  - Female predominance decreases after age 65.
  - Historically diarrhea and abdominal pain most are the most common symptoms.
  - Dermatitis herpetiformis is rare.
Dermatitis Herpetiformis

A skin blister on the elbow of a subject with dermatitis herpetiformis.
Diagnosis

- Often misdiagnosed as IBS.

- Increased surveillance among higher risk groups
  - Down Syndrome, Turner’s Syndrome, Type 1 Diabetes.
  - Rate of diagnosis increased to 43% in one case study.
Differential Diagnosis of Gluten-Related Disorders

Suggestive history, physical examination, and initial evaluation; consider differential diagnosis

Wheat allergy

Specific skin-prick tests
Wheat-specific serum IgE test
Gluten challenge

Tests and challenge positive
No → Rule out wheat allergy
Yes → Confirm wheat allergy

Celiac disease or gluten sensitivity

tTG IgA test (with or without EMA) plus total IgA
Deamidated AGA IgA and IgG tests

Positive tTG, deamidated AGA, or both
No → Strong clinical suspicion
Yes → Perform EGD with biopsy

No → Perform double-blind gluten challenge
Yes → Confirm celiac disease

No → Consider gluten sensitivity
Yes → Confirm gluten sensitivity

Rule out gluten sensitivity; consider other diagnoses
# Serologic Tests

## Table 1. Serum Tests for the Diagnosis of Celiac Disease.*

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (Range)</th>
<th>Specificity (Range)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA anti-tTG antibodies</td>
<td>&gt;95.0 (73.9–100)</td>
<td>&gt;95.0 (77.8–100)</td>
<td>Recommended as first-level screening test</td>
</tr>
<tr>
<td>IgG anti-tTG antibodies</td>
<td>Widely variable (12.6–99.3)</td>
<td>Widely variable (86.3–100)</td>
<td>Useful in patients with IgA deficiency</td>
</tr>
<tr>
<td>IgA antiendomysial antibodies</td>
<td>&gt;90.0 (82.6–100)</td>
<td>98.2 (94.7–100)</td>
<td>Useful in patients with an uncertain diagnosis</td>
</tr>
<tr>
<td>IgG DGP</td>
<td>&gt;90.0 (80.1–98.6)</td>
<td>&gt;90.0 (86.0–96.9)</td>
<td>Useful in patients with IgA deficiency and young children</td>
</tr>
<tr>
<td>HLA-DQ2 or HLA-DQ8</td>
<td>91.0 (82.6–97.0)</td>
<td>54.0 (12.0–68.0)</td>
<td>High negative predictive value</td>
</tr>
</tbody>
</table>

* Data are from Husby et al. and Giersiepen et al. DGP denotes deamidated gliadin peptides, and tTG tissue transglutaminase.
Interpretation of Antibody Tests

- The most sensitive antibody tests are the IgA class.
- Antigliadin no longer though sensitive enough to diagnose celiac disease in adults.
- The diagnostic standard is still the antiendomysial – approaches 100% accuracy but expensive.
- Tissue transglutaminase - > 90% accuracy but less expensive.
Interpretation of Antibody Tests

- Titers of endomysial and anti-tissue transglutaminase correlate with mucosal damage.

- Warning: IgA deficiency is 10 fold higher in this population – beware of false negatives.

- Check total IgA level in patients with a high clinical suspicion of disease-second line test.
Diagnosis Requirements

A duodenal biopsy showing:

- Intraepithelial lymphocytosis
- Crypt hyperplasia
- Villous atrophy

Biopsy confirmation is essential.

Positive response to a gluten free diet.
Who Should be Biopsied?

- Chronic Diarrhea of unknown etiology.
- Iron Deficiency Anemia
- Weight loss
Differential Diagnosis

Table 1. Causes of Villous Atrophy Other Than Celiac Disease.

- Giardiasis
- Collagenous sprue
- Common-variable immunodeficiency
- Autoimmune enteropathy
- Radiation enteritis
- Whipple's disease
- Tuberculosis
- Tropical sprue
- Eosinophilic gastroenteritis
- Human immunodeficiency virus enteropathy
- Intestinal lymphoma
- Zollinger–Ellison syndrome
- Crohn's disease
- Intolerance of foods other than gluten (e.g., milk, soy, chicken, tuna)

Treatment of Celiac Disease

• Nutritional therapy is the only accepted treatment.
• Lifelong elimination of wheat, rye and barley.
• Oats not uniformly recommended because of contamination in growing, transportation and milling.
• Screening for osteoporosis.
• Testing and replacement of micronutrients:
  • Iron, vitamin B12, fat-soluble vitamins and calcium.
### Table 2. Fundamentals of the Gluten-free Diet.

**Grains that should be avoided**
Wheat (includes spelt, kamut, semolina, triticale), rye, barley (including malt)

**Safe grains (gluten-free)**
Rice, amaranth, buckwheat, corn, millet, quinoa, sorghum, teff (an Ethiopian cereal grain), oats

**Sources of gluten-free starches that can be used as flour alternatives**
Cereal grains: amaranth, buckwheat, corn (polenta), millet, quinoa, sorghum, teff, rice (white, brown, wild, basmati, jasmine), montina (Indian rice grass)
Tubers: arrowroot, jicama, taro, potato, tapioca (cassava, manioc, yucca)
Legumes: chickpeas, lentils, kidney beans, navy beans, pea beans, peanuts, soybeans
Nuts: almonds, walnuts, chestnuts, hazelnuts, cashews
Seeds: sunflower, flax, pumpkin
Response to Diet

• Clinical response within days to weeks.

• Histologic recovery can be weeks to years.

• Clinical or histologic improvement fails in – 7 to 30%.

• The most common cause is dietary nonadherence.
<table>
<thead>
<tr>
<th>Table 3. Problems of Dietary Adherence and Poor Response in Celiac Disease.</th>
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<tbody>
<tr>
<td><strong>Reasons for poor adherence to a gluten-free diet</strong></td>
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<tr>
<td>High cost</td>
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<tr>
<td>Poor availability of gluten-free products (in developing countries)</td>
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<tr>
<td>Poor palatability</td>
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<tr>
<td>Absence of symptoms when dietary restrictions not observed</td>
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<tr>
<td>Inadequate information on gluten content of food or drugs</td>
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<tr>
<td>Inadequate dietary counseling</td>
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<tr>
<td>Inadequate initial information supplied by diagnosing physician</td>
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<tr>
<td>Inadequate medical or nutritional follow-up</td>
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<tr>
<td>Lack of participation in a support group</td>
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<tr>
<td>Inaccurate information from physicians, dietitians, support groups, or Internet</td>
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<tr>
<td>Dining out of the home</td>
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<tr>
<td>Social, cultural, or peer pressures</td>
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<tr>
<td>Transition to adolescence</td>
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<tr>
<td>Inadequate medical follow-up after childhood</td>
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<tr>
<td><strong>Causes of poorly responsive celiac disease</strong></td>
</tr>
<tr>
<td>Incorrect diagnosis</td>
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<tr>
<td>Gluten ingestion (intentional or unintentional)</td>
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<tr>
<td>Microscopical colitis</td>
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<tr>
<td>Lactose intolerance</td>
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<tr>
<td>Pancreatic insufficiency</td>
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<tr>
<td>Bacterial overgrowth</td>
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<tr>
<td>Intolerance of foods other than gluten (e.g., fructose, milk, soy)</td>
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<tr>
<td>Inflammatory bowel disease</td>
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<tr>
<td>Irritable bowel syndrome</td>
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<tr>
<td>Anal incontinence</td>
</tr>
<tr>
<td>Collagenous sprue</td>
</tr>
<tr>
<td>Autoimmune enteropathy</td>
</tr>
<tr>
<td>Refractory celiac disease (with or without clonal T cells)</td>
</tr>
<tr>
<td>Enteropathy-associated T-cell lymphoma</td>
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</tbody>
</table>
Refractory Celiac Disease

• Occurs in 5% of patients despite strict adherence to diet.
• Persistent symptoms and villous atrophy.
• Two types:
  Type 1
  Normal intraepithelial lymphocytes

Type 2
Clonal expansion of aberrant intraepithelial lymphocytes
Assessment Plan for patient with poorly responsive celiac disease

Poorly responsive celiac disease

Exclusion of other causes of villous atrophy

Assessment of adherence to gluten-free diet

Good adherence

Evaluation
- Exclusion of bacterial overgrowth and pancreatic insufficiency
- Upper gastrointestinal endoscopy or colonoscopy and biopsy
- Intraepithelial-lymphocyte phenotype on duodenal biopsy
- Enteroscopy (push or push-pull)
- Abdominal radiology (small bowel studies and CT scan)
- Video-capsule endoscopy

Adenocarcinoma

Enteropathy-associated T-cell lymphoma

Refractory celiac disease

Poor adherence

Dietary counseling
- Referral to support group
- Regular follow-up by experienced dietitian

Normal intraepithelial-lymphocyte phenotype (type 1)

Abnormal clonal intraepithelial-lymphocyte phenotype (type 2)
Treatment of Refractory Celiac Disease

Type 1
- Corticosteroids usually induce remission.
- Other immunosuppressive drugs.

Type 2
- High risk for:
  - Ulcerative jejunitis
  - Enteropathy-associated T-cell lymphoma
Complications of Celiac Disease

Adenocarcinoma of the small intestine
  • Twice the risk of the general population

T-cell or B-cell Lymphoma
  • Intestinal or extraintestinal

Oropharyngeal, esophageal and colon Adenocarcinoma

Pancreatic and hepatobiliary cancers

Gluten Sensitivity vs. Celiac Disease

- Many people report gluten sensitivity and a response to a gluten-free diet.
- Media attention to the adverse effects of gluten on health promotes a gluten-free diet without medical supervision.
- Response to therapy alone is not diagnostic.
- Patients with wheat allergy and gluten sensitivity may benefit.

<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 adaptive 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 97% of positive cases)</td>
<td>Not restricted to HLA-DQ2 or HLA-DQ8 (HLA-DQ2–positive, HLA-DQ8–positive, or both in 50% of patients)</td>
<td>Not restricted to HLA-DQ2 or HLA-DQ8 (HLA-DQ2–positive, HLA-DQ8–positive, or both in 35–40% of patients, similar to the general population)</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>Almost always present</td>
<td>Always absent</td>
<td>Always absent</td>
</tr>
<tr>
<td>Enteropathy</td>
<td>Almost always present</td>
<td>Always absent (slight increase in the intraepithelial lymphocyte count)</td>
<td>Always absent (eosinophils in the lamina propria)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Both intestinal and extraintestinal; gastrointestinal symptoms not distinguishable from those of gluten sensitivity and wheat allergy</td>
<td>Both intestinal and extraintestinal; gastrointestinal symptoms not distinguishable from those of celiac disease and wheat allergy</td>
<td>Both intestinal and extraintestinal; gastrointestinal symptoms not distinguishable from those of celiac disease and gluten sensitivity symptoms</td>
</tr>
<tr>
<td>Complications</td>
<td>Coexisting conditions; long-term complications</td>
<td>Absence of coexisting conditions and long-term complications</td>
<td>Absence of coexisting conditions; short-term complications (including anaphylaxis)</td>
</tr>
</tbody>
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Gluten-Related Disorders

Suggestive history, physical examination, and initial evaluation; consider differential diagnosis

Wheat allergy

Specific skin-prick tests
Wheat-specific serum IgE test
Gluten challenge

Tests and challenge positive↓ No → Rule out wheat allergy

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Yes → Consider other diagnoses

Perfom EGD with biopsy

Biopsy positive↓ No → Consider gluten sensitivity

Yes → Perform double-blind gluten challenge

Yes → Confirm celiac disease

Biopsy positive↓ No → Perform EGD with biopsy

Yes → Confirm gluten sensitivity

Rule out gluten sensitivity; consider other diagnoses
Summary of Celiac Disease

- Once considered a GI disorder of children
- Now known to affect different ages, races and ethnic groups.
- IgA anti-tissue transglutaminase is the preferred initial screening test
- Diagnosis confirmed by duodenal biopsy
- Cornerstone of treatment is a gluten-free diet
- Gluten sensitivity may occur in the absence of celiac disease.