CELIAC DISEASE: It’s Everywhere

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Celiac Disease

There is a kind of chronic indigestion which is met in persons of all ages…it may be found in adults who have never left our island.

...nothing unnatural can be seen in the intestine. Whether atrophy of the glandular crypts is present, I cannot tell.

If the patient be cured at all it must be by means of diet...The allowance of farinaceous foods must be small.

Samuel Gee 1888.

Celiac Disease

Definition

Celiac sprue is a T cell mediated enteropathy induced by dietary gluten in genetically predisposed individuals. Once initiated the disease is lifelong. It is characterized by villous atrophy, increased intraepithelial lymphocytes, extensive surface cell damage, and infiltration of the lamina propria with inflammatory cells.
Pathogenesis of Celiac Sprue

Neutral Glutamines
G-X-P

T-cell receptor

HLA-DQ2

Neg charged glutamic acid

T-cell receptor

HLA-DQ2

Normal Small Bowel
Celiac Disease

Untreated Celiac Disease
Celiac Disease

• Celiac disease was once considered a rare GI disorder affecting white children.
• It is now known to affect persons of different ages, races, and ethnic groups.
• It may present with no gastrointestinal symptoms.
• It is widely underdiagnosed.

Genetic Predisposition

• Celiac disease is an HLA-associated condition.
• The primary association is with the HLA heterodimers DQ2 (90%) and DQ8 (10%).
• Gluten sensitive T cells recognize gluten derived peptide when presented in association with DQ2 or DQ8.
• Early exposure to gluten and HLA-DQ2 or DQ8 promote celiac disease development.
**HLA Testing**

<table>
<thead>
<tr>
<th>DQ Genotype</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DQ 2</strong> homozygous</td>
<td>31X</td>
</tr>
<tr>
<td>DQ2/other high risk gene</td>
<td>16X</td>
</tr>
<tr>
<td>DQ2/DQ8</td>
<td>14X</td>
</tr>
<tr>
<td>DQ8 homozygous</td>
<td>10X</td>
</tr>
<tr>
<td>DQ2 heterozygous</td>
<td>10X</td>
</tr>
<tr>
<td>DQ8 heterozygous</td>
<td>2X</td>
</tr>
<tr>
<td>DQ2-, DQ8-</td>
<td>&lt;0.1X</td>
</tr>
</tbody>
</table>


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**Genetic Predisposition**

- 30% of the population of the US and Europe are DQ2 or DQ8 positive.
- DQ2 or DQ8 haplotypes are necessary but not sufficient for celiac disease development.
- At least 39 non-HLA genes confer a predisposition to the disease.
- Approximately 60% of the susceptibility is related to non-HLA genes.
Prevalence

- Until recently, prevalence felt to be 1:300 in Western Ireland to 1:6000 in North America.
- Recent European studies using serologic screening show a prevalence of 1:100 to 1:300 in European countries including Ireland, UK, Sweden, Finland, and Italy.
- The disease is also found in North Africa (1:157 school children in Tunisia), the Middle East, Northwest India, and South America. Cases have been reported from China.
- Recent US studies suggest a prevalence of approximately 1% (3 million Americans).
- Less than 5% of cases in the US currently diagnosed.

Prevalence of Celiac Disease in the United States

- Multicenter study with total of 13,145 subjects studied including 4126 subjects not at risk and 9019 at risk.
- Age distribution corresponded to the age distribution of the 2000 census. 94% were white.
- IgA and IgG AGA, and IgA EMA were measured. Blood of EMA + subjects tested for DQ2 and DQ8 haplotypes.

Prevalence of Celiac Disease in the United States

- 2.7% of subjects positive for EMA. All were positive for TTG and DQ2 or DQ8. Biopsies abnormal in all 350 patients biopsied.
- 41% of EMA + subjects were asymptomatic. Only 35% had diarrhea.
- 27 of 2845 not at risk subjects were EMA + (1:105).
- 1st and 2nd degree relatives of patients with CD had a prevalence of EMA of 1:22 (OR 1.8) and 1:39 (OR 1.7).
- 1:68 symptomatic adults and 1:22 symptomatic children were EMA +.
- Prevalence of celiac disease among minorities was 1:236.


Increased Prevalence and Mortality in Undiagnosed CD

- Sera from 9,133 healthy young adults collected at an AFB from 1948 to 1954 were tested for TTG and , if positive, for EMA. Survival was measured for a period of 45 years.
- Two control cohorts from Minnesota were controls. 5,558 with a similar DOB, and 7,210 with a similar age at sampling.
- In the AF cohort 0.2% had undiagnosed CD. Undiagnosed CD was found in 0.9% of those with similar age and 0.8% in those with similar birth date (4 fold increase, p<0.001).
- During the 45 year follow-up, there was a 4 fold increased risk of death in undiagnosed CD.

Why Is Celiac Disease Not Diagnosed More Frequently?

- Physicians believe that celiac disease is rare and therefore don’t test for it.
- Physicians fail to appreciate that CD may present without GI symptoms.
- Failure by pathologists to recognize early biopsy findings (Marsh 1&2).
- Failure of at risk patients to seek testing.
- Failure to associate symptoms or findings with CD (average gap of 11 years between 1st symptoms and diagnosis in US*).


Characteristics of Adult Celiac Disease in US

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis Considered Prompt</td>
<td>54</td>
</tr>
<tr>
<td>Consultation of &gt; 2 gastroenterologists</td>
<td>27</td>
</tr>
<tr>
<td>Consultation of &gt; 4 gastroenterologists</td>
<td>4</td>
</tr>
<tr>
<td>Prior Diagnosis of IBS</td>
<td>36</td>
</tr>
<tr>
<td>Diagnosing MD Considered Knowledgeable About Diagnosis</td>
<td>20</td>
</tr>
<tr>
<td>Treatment</td>
<td>32</td>
</tr>
<tr>
<td>Follow-up Care</td>
<td>49</td>
</tr>
<tr>
<td>Mean Duration of Symptoms Before Diagnosis</td>
<td>11 years</td>
</tr>
<tr>
<td>Diagnosis in Childhood*</td>
<td>6</td>
</tr>
</tbody>
</table>

*62% went off diet and were rediagnosed as adults.
The Celiac Iceberg

The majority of cases of celiac disease go clinically undetected with either silent or latent disease.


Classic Presentation

- Onset of symptoms frequently occurs between 3-18 months (introduction of weaning foods).
- Children present with failure to thrive, diarrhea, muscle wasting, abdominal distension. Stools are pale, loose and bulky.
- Older children may present with growth retardation and tetany.
- Adults present with diarrhea, steatorrhea, weight loss, iron deficiency, and folate deficiency.
Atypical Presentation

- More cases of celiac sprue are being recognized in adults.
- 20% of cases are first diagnosed in patients older than 60.
- More than 50% of patients with newly diagnosed celiac sprue do not present with gastrointestinal symptoms.

Fasano A. Gastroenterology 2001; 120: 535.

Atypical Presentations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatitis Herpetiformis</td>
<td>CD found in 100% of cases</td>
</tr>
<tr>
<td>Iron Deficiency Anemia</td>
<td>Refractory to oral iron</td>
</tr>
<tr>
<td>Idiopathic Short Stature</td>
<td>9-10% of patients may have CD</td>
</tr>
<tr>
<td>Dental Enamel Hypoplasia</td>
<td>Found in 30% of untreated CD</td>
</tr>
<tr>
<td>Arthritis and Arthralgia</td>
<td>CD found in 1.5-7.5% of RA pts</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Low bone mineral density universal</td>
</tr>
<tr>
<td>Neurologic Problems</td>
<td>Peripheral neuropathy, demyelinating CNS lesions, seizures, ataxia</td>
</tr>
</tbody>
</table>
Dental Enamel Defects

• Only the permanent dentition is involved
• May be the *only* presenting sign of celiac disease

Dermatitis Herpetiformis
A 53 year old man was referred for colonoscopy because of iron deficiency anemia.

He gave a history of dermatitis herpetiformis of 35 years duration treated with dapsone.

Colonoscopy was normal.

The patient was told he had celiac disease since 100% of people with DH have celiac disease, and this was the likely explanation of his anemia.

He was given information on the gluten free diet, referred to a dietician, and given contact information for the local CSA chapter.
Case 1 DH

- He represented 2 years later with worsening anemia despite oral iron. He did not follow a GFD because his internist and dermatologist told him he didn’t have celiac disease since he had no diarrhea.
- Height was 6 feet, one inch, and BMI 21. Hgb was 11.2g/dL, ferritin 3, iron saturation 8%. Anti-TTG IgA was 23 (nl <3), and anti-gliadin antibody IgA 71 (nl <20). EGD showed a mosaic pattern with scalloping and duodenal biopsies confirmed celiac disease.
- On a GFD with oral iron replacement his anemia resolved, and he gained 15 pounds in weight. Anti-gliadin and TTG antibodies were no longer detectable.

Other Associated Extraintestinal Manifestations

- Delayed Puberty
- Recurrent Abortions
- Reduced Fertility
- Aphthous Ulcers
- Chronic Hepatitis
- Splenic Atrophy
### Bone Disease in Celiacs

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>100</td>
<td>322</td>
</tr>
<tr>
<td>Metabolic Bone Disease</td>
<td>69</td>
<td>222</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>70</td>
<td>21/30</td>
</tr>
<tr>
<td>Premenopausal Female</td>
<td>60</td>
<td>49/81</td>
</tr>
<tr>
<td>Postmenopausal Female</td>
<td>86</td>
<td>59/68</td>
</tr>
<tr>
<td>Minor Villous Atrophy</td>
<td>63</td>
<td>-</td>
</tr>
</tbody>
</table>

Goerres MS. Gastroenterology 2002.

### Increased Prevalence of Celiac Disease in Osteoporosis

- 266 patients with osteoporosis and 574 controls studies were studied with TTG antibodies, and if positive biopsy.
- Nine osteoporotic patients (3.4%) and 1 control (0.2%) had biopsy documented CD.
- The anti-TTG level correlated with the severity of the osteoporosis.
- Treatment of CD with a GFD for 1 year resulted in a marked improvement in T scores.

Autoimmune Disorders Associated with Celiac Disease

- Dermatitis Herpetiformis
- Type 1 DM
- Autoimmune Thyroiditis
- Sjogren Syndrome
- Addison Disease
- Autoimmune Atrophic Gastritis
- Rheumatoid Arthritis

Case 2 RA

- A 42 year old woman was diagnosed as having celiac disease at age 9 months. She followed a GFD throughout childhood with resolution of symptoms. She reverted to a regular diet at age 15 with no recurrence of symptoms.
- The patient was referred by her rheumatologist for evaluation of diarrhea and weight loss at age 42. She had severe rheumatoid arthritis and anemia requiring intermittent iron infusions.
Case 2 RA

- Height was 5 feet, 7 inches. BMI 18. Angular cheilitis, and active inflammation of multiple joints was noted.
- Hemoglobin was 11.2 g/dL, ferritin 7, MCV 77, and B12 369. EGD showed scalloping of folds and biopsies showed villous atrophy consistent with celiac disease.
- The patient responded to a gluten free diet with improvement in diarrhea, and anemia. At age 62 she became refractory to dietary therapy and required therapy with steroids and immunomodulators.

Diagnosis

- Requires an awareness of the disease and its multiple presentation.
- Small bowel biopsy is still the gold standard
- Serology useful in case finding
- HLA genotyping
- Capsule endoscopy
Serologic Tests

<table>
<thead>
<tr>
<th>Serologic Test</th>
<th>Sens %</th>
<th>Spec %</th>
<th>PPV %</th>
<th>NPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigliadin Ab (IgA)</td>
<td>75-90</td>
<td>82-95</td>
<td>28-90</td>
<td>65-90</td>
</tr>
<tr>
<td>Antigliadin Ab(IgG)</td>
<td>69-85</td>
<td>82-95</td>
<td>20-90</td>
<td>41-88</td>
</tr>
<tr>
<td>Antiendomysial Ab</td>
<td>85-98</td>
<td>97-100</td>
<td>98-100</td>
<td>80-95</td>
</tr>
<tr>
<td>Transglutaminase (IgA ELISA)</td>
<td>95-98</td>
<td>94-95</td>
<td>91-95</td>
<td>96-98</td>
</tr>
</tbody>
</table>

Case 3
Role of Serology

- A 57 year old woman was referred for SOM. She had a cholecystectomy in 1997 without pain relief. In 2009 she was evaluated with an MRI showing a CBD of 13 mm in diameter. A sphincterotomy was done but no stones were retrieved and her pain persisted.
- She complained of epigastric discomfort lasting as long as several hours after meals. This was accompanied by nausea, gas and bloating. She had a ten pound weight loss in the last six months but no diarrhea or steatorrhea.
Case 3
Role of Serology

• LFTs, amylase and lipase were normal. TTG IgA was 30 IU (normal <5), and anti-gliadin IgA was 35 U (normal <11).
• EGD revealed a mosaic pattern in the duodenum and biopsies were compatible with celiac disease showing increased IELs, moderate to severe villous blunting, and an expanded lamina propria with a lymphoplasmocytic infiltrate.
• After three weeks of a gluten free diet, the patient had noted a marked improvement in symptoms.
Case Finding in Celiac Disease

- Multicenter study of active case finding in primary care.
- All individuals with symptoms or conditions associated with CD tested for TTG antibodies.
- +TTG in 30 out of 976 patients tested (3.1%). CD confirmed in 22 (prevalence 2.25%). Only 6 had diarrhea.
- Baseline diagnosis rate for CD was 0.27/1000. Rate increased to 11.6/1000 with active case finding (p<0.001).

Who Should Be Tested?

- Patients with typical symptoms.
- Patients with unexplained deficiency states.
- Patients with associated diseases (Type 1 diabetes, thyroiditis, rheumatoid arthritis, autoimmune hepatobiliary disease, ataxia, neuropathy, Down’s syndrome, Turner’s syndrome).
- Relatives of patient’s with celiac disease.

NIH Consensus Conference 2004

Screening Relatives

- Initially test for HLA DQ2 or HLA DQ8 to identify those at risk.
  - Test positive individuals with tTG antibodies.
  - Antibody positive patients should have small bowel biopsy for definitive diagnosis.
- In DQ2 or DQ8 positive individuals, an initial negative tTG does not preclude later development of CD and repeat testing is recommended.
- The optimal frequency of repeat testing has not been determined.
Further Testing

• For those who have been placed on a gluten free diet longer than 2 months without an appropriate diagnostic evaluation, testing should follow a gluten challenge 3-4 weeks).
• For those who decline a gluten challenge, HLA DQ2 and DQ8 typing may help exclude the diagnosis.

Management of Celiac Disease

• Gluten free diet for life
• Identification and treatment of nutritional deficiencies
• Access to an advocacy group
• Continuous and long term follow up
Gluten Free Diet

1. Avoid: Wheat, rye and barley. Oats may be tolerated.
2. Substitute: Rice, corn, potato, soy, and tapioca
3. Gluten free foods contain < 20 ppm of gluten. Safe level of gluten per 24 hours < 10 mg.
4. Problems:
   Compliance.
   Widespread use of gluten.
   Contamination of other grains with wheat flour dust.

Diet Adherence and Age at Diagnosis

- Highest rates of adherence are in patients diagnosed at a young age
  - Sweden (adults)
    - Age at diagnosis <4 years: 80%
    - Age at diagnosis >4 years: 36%
  - France and Belgium (adults)
    - <50% after 1 year

Mild Enteropathy

• 23 patients with mild enteropathy (Marsh I &II) studied for 1 year.
• Randomized to GFD (13) or continued regular diet (10).
• In GFD group symptoms resolved, antibody titers (EMA) decreased or became negative.
• In regular diet group, villous architecture deteriorated in all, and symptoms and antibody titers persisted.


Long Term Outcome In Patients Resuming Normal Diet

• 34 patients, mean age 25 resumed normal diet for a mean of 14 years.
• 20/34 were symptom free. 14/34 had diarrhea.
• Signs of malabsorption occurred in 66% (anemia 12%, iron deficiency 61%, hypocalcemia 27%, osteopenia 55%).
• 79% had villous atrophy, remaining 21% had increased IELs (>40/100 enterocytes).

Grosdedin E. Gastroenterology 2002.
Complications of Celiac Disease

- Refractory sprue
  - Ulcerative jejunitis (mortality 30%)
  - Intestinal lymphoma (enteropathy associated T-cell lymphoma, RR=40-876)
- B-cell NHL (RR=7)
- Small intestinal adenocarcinoma (RR 83-240)
- Other cancers of the GI tract
- All cause mortality is about two times control populations


Ulcerative Jejunitis
Ulcerative Jejunitis

T-Cell Lymphoma
Refractory Sprue

• Primary or secondary failure to respond to a gluten free diet with persistent villous atrophy.
• RCD I - normal intraepithelial lymphocyte phenotype.
• RCD II – abnormal phenotype of intraepithelial lymphocytes with clonal rearrangement of the TCR gamma or delta chain.
• RCD II characterized by ulcerative jejunitis, malnutrition, and lymphocytic gastritis.

Treatment of RCD

• Persistent symptoms: Confirm diagnosis. Look for microscopic colitis, and exclude autoimmune enteropathy.
• Suspicious for RCD: Evaluate for overt malignancy (lymphoma or carcinoma).
• Classify as RCD I or II: Determine presence of aberrant intraepithelial lymphocytes (flow cytometry or immunostaining).
Treatment of RCD

RCD I
- Strict GFD
- Parenteral nutrition
- Budesonide
- Prednisone alone
- Prednisone + azathioprine

RCD II
- Strict GFD
- Parenteral nutrition
- Budesonide
- Prednisone
- Cladribine IV (?)
- Avoid azathioprine
- High dose chemo followed by ASCT

Incidence and Spectrum of Refractory Celiac Disease

- Records of 844 patients with CD seen at the Beth Israel Deconess Medical Center Celiac Center reviewed.
- 34/844 (4%) had RCD.
- 1.5% of patients diagnosed at this center had RCD.
- 5 patients (14.7%) had RCD type 2 and two of these died from EATL within 24 months of diagnosis of CD.

Bakht R. Am J Gastroenterol 2011; 106: 923.
Case 4 RCD I

- A 28 year old Hispanic man presented with watery, non-bloody diarrhea, and a twenty pound weight loss. His height was 5 ft 3 inches and weight 110 pounds. Initial labs revealed a hemoglobin of 10.9 g/dL, low ferritin and iron levels, and INR of 9.8.
- After correction of the INR and 10 days of TPN, a duodenal biopsy was done and showed active celiac disease with total villous atrophy.
- When first seen at USF, he had continued diarrhea and easy fatiguability despite a gluten free diet. Hgb was 12.9 g/dL, ferritin 21, and MCV 77. PT and PTT were normal. Anti-TTG was 106 units (normal <3) and anti-gliadin IgA antibody was 65 (normal <20). Bone densitometry showed osteopenia.

- He was advised to continue a gluten free diet, begin a low lactose diet, and was started on pancreatic enzymes. He did not improve.
- Then started on budesonide with dramatic improvement of diarrhea and some weight gain. When Entocort was discontinued, symptoms recurred.
- After nine months of a poor response to diet he was started on Imuran with a gradual increase in dose to 125 mg daily.
- On Imuran he had one bowel movement daily, and weight increased to 138 pounds (highest ever). Despite this, biopsies 5 years after diagnosis showed continued villous atrophy, but no evidence of EATL. He was totally off steroids.
Microscopic Colitis

- Found in approximately 30% of patients with celiac disease and does not respond to a gluten free diet.
- 2% to 10% of patients with microscopic colitis have villous atrophy suggestive of celiac disease
- A low threshold for celiac disease screening among patients with microscopic colitis is warranted.


Celiac Sprue

- Underdiagnosed with a prevalence of 1% in US.
- More than half of patients are diagnosed as adults. Frequently non-GI symptoms predominate.
- New serologic tests are relatively sensitive and specific.
- Gluten free diet should be lifelong and appears to prevent complications including T-cell lymphoma.