Celiac Sprue

Samuel C Somers MD MMSc
May 2015
• Celiac Disease
• Sprue
• Gluten-enteropathy
• Celiac sprue

Inflammatory disease of the small bowel with a known trigger

Same Disease
History of Celiac Disease
History of Celiac

- Cereal grains were first domesticated from wild grasses in the Fertile Crescent about 10,000 years ago
History of Celiac

Aretaeus from Cappadochia (now Turkey) in the 2nd century AD described a chronic malabsorptive condition. He named this disorder "koiliakos" which is Greek for "suffering in the bowels."

The second classical description was in 1888 in a report entitled "On the Coeliac Affection" by Samuel Gee:

"to regulate the food is the main part of treatment ... The allowance of farinaceous foods must be small ... but if the patient can be cured at all, it must be by means of diet."

S. Gee: "On the coeliac affection" Saint Bartholomew's Hospital Reports, London, 1888, 24: 17-20
History of Celiac

- During World War II, celiac children improved during the food shortages when bread was unavailable.
- After the war, symptoms reoccurred when bread and cereals were reintroduced.
- Dutch pediatrician Willem K Dicke recognized and confirmed this association between cereal grains and malabsorption.

DICKE, WK, WEIJERS, HA, VAN DE, KAMER JH. Coeliac disease. II. The presence in wheat of a factor having a deleterious effect in cases of coeliac disease. Acta Paediatr 1953; 42:34.
The celiac lesion in the proximal small intestine was first described by Paulley in 1954.

It was learned that celiac disease and adult non-tropical sprue share many of the same features.

These classic findings are:
- mucosal inflammation
- crypt hyperplasia
- villous atrophy
Prevalence of Celiac Disease
## Prevalence by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence</th>
<th>Population</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Croatia</td>
<td>1:526</td>
<td>Children</td>
<td>EMA</td>
</tr>
<tr>
<td>USA</td>
<td>1:57</td>
<td>Children</td>
<td>EMA+Bx</td>
</tr>
<tr>
<td>Brazil</td>
<td>1:667</td>
<td>Blood donors</td>
<td>EMA+Bx</td>
</tr>
<tr>
<td>Italy</td>
<td>1:400</td>
<td>Blood donors</td>
<td>EMA+Bx</td>
</tr>
<tr>
<td>UK</td>
<td>1:38</td>
<td>Adults</td>
<td>EMA+Bx</td>
</tr>
<tr>
<td>Spain</td>
<td>1:389</td>
<td>Adults</td>
<td>EMA+Bx</td>
</tr>
<tr>
<td>Ireland</td>
<td>1:19</td>
<td>Adults</td>
<td>Bx</td>
</tr>
<tr>
<td>Italy</td>
<td>1:86</td>
<td>Adults</td>
<td>Bx</td>
</tr>
<tr>
<td>USA</td>
<td>1:194</td>
<td>Adults</td>
<td>Bx</td>
</tr>
</tbody>
</table>
Prevalence of Celiac Disease

- In some studies, the prevalence of celiac disease was as follows:
  - 1:22 in first-degree relatives
  - 1:39 in second-degree relatives
  - 1:56 in symptomatic patients
  - 1:133 in the not-at-risk groups

CELIAC ICEBERG

Diagnosed

Classical Clinical Manifestations

Undiagnosed

Small Intestine Morphology

Silent Celiac Disease

Latent Celiac Disease

Healthy Population

Atypical Clinical Manifestations

Genetic Susceptibility
Pathophysiology of Celiac Disease

- Celiac disease is an immune disorder that is triggered by an environmental agent (the gliadin component of gluten) in genetically predisposed individuals.

Celiac Disease - Trigger

- **Family**: Gramineae
- **Subfamily**: Festucoideae
- **Tribe**: Triticeae, Aveneae, Oryzae, Andropogoneae
  - **Wheat Rye Barley**: Gliadin, Secalin, Hordein
  - **Oats**: Avenin, Gin
  - **Rice**: Gin, Leu + Ala
  - **Maize Sorghum**: Leu + Ala

**Alcohol-soluble prolamin**

**Amino acid predominance**
Pathophysiology of Celiac Disease

- The pathophysiology of gliadin toxicity in celiac patients is poorly understood.
Pathophysiology of Celiac Disease

- The current hypotheses:
  - Gliadin-sensitive T cells in genetically predisposed individuals recognize gluten-derived peptide epitopes and develop an inflammatory response which produces mucosal damage.

Nilsen, EM, Lundin, KE, Krajci, P, et al. Gluten specific, HLA-DQ restricted T cells from coeliac mucosa produce cytokines with Th1 or Th0 profile dominated by interferon gamma. Gut 1995; 37:766
Celiac Disease: Clinical Manifestations in Children

The classical presentation is in children after weaning and introduction of cereals into the diet:

- Failure to thrive
- Apathy
- Pallor
- Anorexia
- Muscle wasting with generalized hypotonia
- Abdominal bloating and distention
- Soft, bulky, clay-colored, offensive stools
CELIAC DISEASE: PEDIATRICS

- Classic presentation
  - Present 1-2 yo after cereals introduced in diet
  - Steatorrhea, vomiting, crampy abdominal pain
  - Failure to thrive, muscle wasting, abdominal distention
Celiac Disease: Clinical Manifestations

- As our understanding of celiac improved and serologic testing has become available, subclinical forms of the disease have been recognized.
Celiac Disease: Clinical Manifestations in Children

<table>
<thead>
<tr>
<th>Symptoms and signs at presentation</th>
<th>Overall prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency with anemia</td>
<td>29</td>
</tr>
<tr>
<td>Iron deficiency without anemia</td>
<td>27</td>
</tr>
<tr>
<td>Recurrent Abdominal Pain</td>
<td>24</td>
</tr>
<tr>
<td>Mood Changes</td>
<td>17</td>
</tr>
<tr>
<td>Recurrent Aphthous Stomatitis</td>
<td>11</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>10</td>
</tr>
<tr>
<td>Recurrent diarrhea</td>
<td>9</td>
</tr>
<tr>
<td>Short stature</td>
<td>7</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
</tr>
<tr>
<td>Pubertal delay</td>
<td>2</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>2</td>
</tr>
</tbody>
</table>

CELIAC DISEASE IS A SYSTEMIC DISEASE

GENERAL
- GROWTH DELAY
- MALIGNANCIES
- ANEMIA

GI
- DIARRHEA
- VOMITING
- DISTENTION
- ABDOMINAL PAIN
- MALNUTRITION
- WEIGHT LOSS
- HEPATITIS
- CHOLANGITIS

BONE
- OSTEOPOROSIS
- ARTHRITIS
- DENTAL

CNS
- ATAXIA
- SEIZURES
- DEPRESSION

HEART
- CARDITIS

SKIN
- DERMATITIS
- HERPETIFORMIS
- APHTHOUS STOMATITIS
- HAIR LOSS

REPRODUCTIVE
- MISCARRIAGE
- INFERTILITY
# ASSOCIATED CONDITIONS

## Extraintestinal features
- Folate deficiency anemia
- Osteopenia/osteoporosis
- Dental enamel hypoplasia
- Vitamin K deficiency
- Hypertransaminasemia
- Thrombocytosis
- Arthralgia/arthropathy
- Polyneuropathy
- Ataxia
- Epilepsy with or without calcifications
- Infertility
- Recurrent abortion
- Anxiety and depression
- Alopecia

## Definite associations
- Dermatitis herpetiformis
- IgA deficiency
- Type I DM
- Autoimmune thyroid disease
- Sjögren’s syndrome
- Microscopic colitis
- Rheumatoid arthritis
- Down’s syndrome
- IgA nephropathy

## Possible associations
- Inflammatory bowel disease
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Addison’s disease
- SLE

## Complications
- Refractory sprue
- Enteropathy-associated T-cell lymphoma
- Carcinoma of the oropharynx, esophagus, and small bowel
- Ulcerative jejunoileitis
- Collagenous sprue
Celiac Disease: Clinical Manifestations in Adults

In a study of 1138 people with biopsy–proven celiac disease:

- Majority of individuals were diagnosed in their 4th to 6th decades.
- Women predominated (2.9:1)- the female predominance was less marked in the elderly.
- Diarrhea was the main presenting symptom occurring in 85%.
- 36% had a previous diagnosis of irritable bowel syndrome.
- Symptoms were present a mean of 11 years before diagnosis.

CELIAC ICEBERG

Diagnosed:
- Classical Clinical Manifestations

Undiagnosed:
- Silent Celiac Disease
- Latent Celiac Disease
- Healthy Population
- Atypical Clinical Manifestations

Small Intestine Morphology

Genetic Susceptibility
Celiac Disease: Clinical Manifestations in Adults

In a population-based study from Minnesota, Murray et al noted a 10-fold increase in the incidence of celiac disease from 1950 to 2001.

- The clinical severity of the disease decreased, with fewer people with diarrhea and weight loss at presentation.
- Only 54% had diarrhea at diagnosis, 34% abdominal pain and 30% bloating.
- Obesity was present in 27%.

Spectrum of Celiac Disease

Few if any GI symptoms

Fatigue
Depression, irritability
Menstrual irregularity
Weakness
Infertility
Growth Disturbance
Neurologic Complaints

Marked GI symptoms

Diarrhea
Bulky, Pale, Foul stools
Abdominal Distension, Bloating
Abdominal cramps
Weight loss
Loss of or increased appetite

KAGNOFF, MF. “Overview and Pathogenesis of Celiac Disease” GASTROENTEROLOGY 2005;128:S10–S18
Classification of Celiac Disease

- Classical celiac disease
- Celiac disease with atypical symptoms
- Silent celiac disease
- Latent celiac disease
Celiac Disease

Clinical Presentation

Classical
- Diarrhea
- Gas/bloating
- Weight loss

Atypical
- Constipation
- Dyspepsia
- Anemia
- Osteoporosis
- Rash
- Neuropathy/ataxia
- Hepatitis
- Dental enamel hypoplasia

Silent
- No sx/signs
- Positive Ab
- Abnormal bx

Latent
- No sx/signs
- Positive Ab
- Normal bx
- OR
- CD in remission
Celiac Disease: Associated Disorders

Dermatitis Herpetiformis
Iron deficiency anemia
Osteoporosis, Osteomalacia and Vitamin D deficiency
Malignancies
Type 1 diabetes
Other autoimmune endocrine disorders
Neuropsychologic Features
Others (Downs syndrome, IgA deficiency, rheumatologic disorders)
Celiac Disease: Dermatitis Herpetiformis

- Symmetric vesicles, crusts and erosions distributed over the extensor areas of the elbows, knees, buttocks, shoulders and scalp, with a tendency to grouping of individual lesions.

PRUESSNER, HT. Detecting Celiac Disease in Your Patients. 1998 by the American Academy of Family Physicians
University of Texas Medical School at Houston
DERMATITIS HERPETIFORMIS
ENDOCRINE DISORDERS

DIABETES MELLITUS

• 1-1.5% of diabetic children have CD
  – Classical symptoms, poor glycemic control, frequent hypoglycemia
  – Associated with HLA-DR1-DQ2 and DR4-DQ8

THYROID DISEASE

– Subclinical hypothyroidism very common
– Increased prevalence of autoimmune thyroid disease
Celiac Disease: Iron Deficiency Anemia

• In a study of 227 patients with biopsy–proven celiac disease- iron-deficiency anemia was the mode of presentation in 8%.

• In a Mayo Clinic study, celiac disease was identified as the cause of iron deficiency in 15% of those undergoing endoscopic assessment for iron deficiency.

• In a prospective study of adults, mean age in their 50s, Karnum et al found 2.8% to have celiac disease.


840 individuals were evaluated by serologic screening for celiac disease at the Washington University Bone Clinic — 266 with osteoporosis — 574 without osteoporosis.

Individuals with positive serologic test were offered endoscopic intestinal biopsy.

The prevalence of biopsy-proven celiac disease was — 3.4% in individuals with osteoporosis — 0.2% in individuals without osteoporosis.
### Celiac Disease: Malignancies

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Overall Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>2 to 3</td>
</tr>
<tr>
<td>Enteropathy - associated T-cell lymphomas</td>
<td>30 to 40 (w/o gluten free diet)</td>
</tr>
<tr>
<td>Small intestinal adenocarcinoma</td>
<td>83</td>
</tr>
<tr>
<td>Mouth, pharynx, esophagus cancer</td>
<td>23 (w/o gluten free diet)</td>
</tr>
</tbody>
</table>

*American Gastroenterological Association, Ciclitra, PJ, Gastroenterology 2001; 120: 1526.*
Diagnosis of Celiac Disease

Clinical Findings

Small Intestinal Mucosal Biopsy

Gluten Re-challenge

Seroologic testing
Normal duodenum

Scalloped folds
Mosaic pattern
Diagnosis: Small Bowel Endoscopy

Normal

Celiac
CAPSULE ENDOSCOPY
Diagnosis: Small Bowel Endoscopy
Other Causes of Villous Atrophy

Bacterial Overgrowth
Crohn’s disease
Cow’s milk protein intolerance (children)
Eosinophilic gastroenteritis
Giardiasis
Lymphoma
Peptic duodenitis
Post gastroenteritis
Tropical sprue
Zollinger Ellison syndrome
Diagnosis of Celiac: Serologic Testing

- **IgA antigliadin antibodies**
  - Sensitivity 80 to 90 %
  - Specificity 85 to 95 %

- **IgA endomysial antibodies**
  - Sensitivity 85 to 98 %
  - Specificity 97 to 100 %

- **IgA tissue transglutaminase antibodies**
  - Sensitivity 90 to 98 %
  - Specificity 95 to 97 %

Kelly, CP. Coeliac disease: Non-invasive tests to screen for gluten sensitive enteropathy and to monitor response to dietary therapy. Dublin University, Trinity College, Dublin 1995.
Management of Celiac Disease

- Gluten avoidance is the mainstay of treatment
- Prior to the introduction of a strict gluten-free diet, prognosis was very poor
- Mortality was 12 percent in one retrospective study of 544 children

Hardwick, C. Prognosis in coeliac disease. Arch Dis Child 1939; 14:279
TREATMENT

GLUTEN FREE DIET

GLUTEN FREE DIET

GLUTEN FREE DIET

GLUTEN FREE DIET
TREATMENT

• Avoid *all* foods containing wheat, rye, & barley
• Consider avoiding foods containing oats, (at least initially)
• Use *only* rice, corn, maize, buckwheat, potato, soybean, or tapioca flours, meals or starches
• Look for foods that have the gluten free symbol
• Read *all* labels and study the ingredients of processed foods
• Avoid *all* beers, lagers, ales, & stouts
• Beware of gluten in medications, food additives, emulsifiers, & stabilizers
• Wine, liquers, most ciders, & other spirits, *including* whiskey & brandy, *are allowed!*

[Image of gluten free symbol]
Management of Celiac Disease

In general, the following advice can be given to all patients:

- Foods containing wheat, rye, and barley should be avoided.
- Soybean or tapioca flours, rice, corn, buckwheat, and potatoes are safe.
- Read labels on prepared foods and condiments carefully (many stabilizers or emulsifiers contain gluten)
- Dairy products may need to be avoided initially- many patients have secondary lactose intolerance.
RESPONSE TO A GLUTEN-FREE DIET

90% IMPROVE (within 2 weeks)

indiscretion

10% FAIL TO IMPROVE

Dietary

Lactose or fructose Intolerance

Microscopic colitis

Wrong Diagnosis

Pancreatic Insufficiency

Bacterial overgrowth

Refractory sprue
Monitoring Adherence by Serologic Testing

- A pretreatment antibody level should be determined at the time of diagnosis.
- Serologic testing is of no use if antibody levels are not elevated prior to therapy.
- Exclusion of gluten from the diet results in a gradual decline in serum IgA antigliadin and IgA tTG levels.
- A normal baseline value is typically reached within three to six months.
- If the levels do not fall as anticipated, the patient may be continuing to ingest gluten either intentionally or inadvertently.

Kelly, CP. Coeliac disease: Non-invasive tests to screen for gluten sensitive enteropathy and to monitor response to dietary therapy. Dublin University, Trinity College, Dublin 1995.
Celiac Disease
Who Should Have Antibody Testing?

Support diagnosis
Screening High risk groups
  First and second degree relatives
  Type I Diabetes Mellitus
  Dermatitis Herpetiformis
  Autoimmune thyroid disease
  Primary Biliary Cirrhosis
  Irritable Bowel Syndrome
  Turner’s and Down’s Syndrome

Syndrome
Celiac Disease
Who Should Undergo Duodenal Biopsy?

- High risk with GI symptoms
- Dermatitis Herpetiformis
- Unexplained iron deficiency anemia
- Early osteoporosis/bone fracture
- Neuropathy/ataxia
- Positive screening antibody test
Celiac Disease: Future Treatments

- Bacterial Prolyl Endopeptidase - taken with meals
- Genetically altered wheat grain
- Specific Inhibitors
  - HLA DQ2
  - tTG
  - IL15
- Tight junction modulators
- Gluten binders - taken with meals
Summary

CELIAC DISEASE

T-cell mediated small bowel mucosa inflammation
Triggered by gluten in the diet in those genetically predisposed
Malabsorption of nutrients
Presents age 2 yrs, young adults, or any age
Diagnosis made by abnormal small bowel biopsy that reverts to normal on a gluten-free diet
Treatment is a life-long strict GF-diet
CONCLUSION

• More common than previously thought
• Presentation can be atypical
• Serologic tests and biopsy for diagnosis
• Associated conditions are numerous and can be affected by treatment
• Gluten-free diet is effective treatment
RESOURCES

Lone Star Celiac Support Group
dfwceliac.org
Celiac Sprue Association
csaceliacs.org
Celiac Disease Foundation
celiac.org
National Institutes of Health
digestive.niddk.nih.gov/ddiseases/pubs/celiac