Celiac Disease: How To Identify A Clinical Chameleon

Alessio Fasano, M.D.
Mucosal Biology Research Center and Center for Celiac Research
University of Maryland School of Medicine

Objectives

• Definition of celiac disease;
• Basic concepts on the pathogenesis of celiac disease;
• Overview of clinical presentations of celiac disease;
• Presentation of the most recent data on the epidemiology of celiac disease;
• Screening strategies to identify celiac disease cases;
• Current and future diagnostic tools for celiac disease;
• Principle of treatment;
• Future therapeutic directions;
• Ongoing research on prevention of celiac disease.

The Banana Babies

WK Dicke, 1905 - 1962
1st case of CD at UMB: 1938
Modern Definition

• Celiac disease is an autoimmune condition
• Occurs in genetically susceptible individuals
  – DQ2 and/or DQ8 positive HLA haplotype is necessary but not sufficient
• A unique autoimmune disorder because:
  – both the environmental trigger (gluten) and the autoantigen (tissue Transglutaminase) are known
  – elimination of the environmental trigger leads to a complete resolution of the disease

Pathogenesis

Genetics

• Several genes are involved
• The most consistent genetic component depends on the presence of HLA-DQ (DQ2 and/or DQ8) genes
• Other genes (not yet identified) account for 60% of the inherited component of the disease
• HLA-DQ2 and/or DQ8 genes are necessary (No DQ2/8, no Celiac Disease!) but not sufficient for the development of the disease
Dietary Factors

The Grass Family - (GRAMINEAE)

Subfamily

Festucoideae

Tribe

Zizaneae Oryzeae Hordeae Aveneae Festuceaea Chlorideae

wild rice rice wheat oat finger millet (ragi) teff

The Holy Trinity of the Autoimmune Mechanisms in Celiac Disease

Fasano A; Scientific American Aug. 2009

The Clinic Outcome of the Holy Trinity: Celiac Iceberg

Symptomatic Celiac Disease

Manifest mucosal lesion

Silent Celiac Disease

Latent Celiac Disease

Normal Mucosa

Genetic susceptibility: - DQ2, DQ8
Positive serology
Gastrointestinal Manifestations
(“Classic”)

Most common age of presentation: 6-24 months

- Chronic or recurrent diarrhea
- Abdominal distension
- Anorexia
- Failure to thrive or weight loss
- Abdominal pain
- Vomiting
- Constipation
- Irritability

Rarely: Celiac crisis

Non Gastrointestinal Manifestations

Most common age of presentation: older child to adult

- Dermatitis Herpetiformis
- Dental enamel hypoplasia of permanent teeth
- Osteopenia/Osteoporosis
- Short Stature
- Delayed Puberty
- Iron-deficient anemia resistant to oral Fe
- Hepatitis
- Arthritis
- Epilepsy with occipital calcifications

Listed in descending order of strength of evidence

Recurrent Aphtous Stomatitis

By permission of C. Mulder, Amsterdam (Netherlands)
Dermatitis Herpetiformis

- Erythematous macule > urticarial papule > tense vesicles
- Severe pruritus
- Symmetric distribution
- 90% no GI symptoms
- 75% villous atrophy
- Gluten sensitive


Anemia in Celiac Disease

Most common non-GI manifestation in adults: 5-8% of adults with unexplained iron deficiency anemia have Celiac Disease

- Microcytic anemia - iron absorption most efficient in the duodenum
- Megaloblastic/Macrocytic anemia – folate is absorbed primarily in the proximal third of the small intestine (location of folate hydrolases)
- Vitamin B-12 deficiency occurs rarely

Osteoporosis

Low bone mineral density improves in children but not in adults (~>30 y old) on a gluten-free diet.
Short Stature/Delayed Puberty

- Short stature in children/teens:
  - ~10% of short children and teens have evidence of celiac disease
- Delayed menarche:
  - Higher prevalence in teens with untreated Celiac Disease

CT Scan Showing Occipital Calcifications in a Boy with Celiac Disease and Epilepsy

Associated Conditions
The Clinical Manifestations of Celiac Disease are More Heterogeneous Than Previously Appreciated


Epidemiology

The "old" Celiac Disease Epidemiology:

- A rare disorder typical of infancy
- Wide incidence fluctuates in space (1/400 Ireland to 1/10000 Denmark) and in time
- A disease of essentially European origin

"Mines" of CD have been found among

- Relatives: short stature, anaemia, fatigue, hypertransaminasemia
- Patients with Associated diseases: autoimmune disorders, Down s, IgA deficiency, neuropathies, osteoporosis, infertility
- "Healthy" groups: blood donors, students, general population
**Celiac Disease Epidemiological Study in USA**

Population screened: 13145

- Healthy Individuals: 4146
- Risk Groups: 8999
  - Symptomatic subjects: 2598
  - 1st degree relatives: 2698
  - 2nd degree relatives: 3041
- Positive: 31
- Negative: 4214

Projected number (conservative) of celiac disease patients in the U.S.A.: 2,615,954

MAJOR PUBLIC HEALTH PROBLEM NATIONWIDE WITH SOME REGIONAL DIFFERENCES


**CD Icebergs**

Data CFCR 2005

<table>
<thead>
<tr>
<th>Country</th>
<th>Overall (X 1000)</th>
<th>Diagnosed (X 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ireland</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Italy</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Netherlands</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Sweden</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>USA</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

**World Health Organization Criteria For Mass Screenings**

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>SATISFIED IN CD?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Early detection of the disease could be difficult on a clinical basis.</td>
<td>YES</td>
</tr>
<tr>
<td>2. The disease must be a common disorder causing significant morbidity in the general population.</td>
<td>YES</td>
</tr>
<tr>
<td>3. The screening tests must be highly sensitive and specific for the target disease.</td>
<td>YES</td>
</tr>
<tr>
<td>4. A treatment for the disease must be available.</td>
<td>YES</td>
</tr>
<tr>
<td>5. If not recognized, the disease could result in severe complications difficult to manage.</td>
<td>YES</td>
</tr>
</tbody>
</table>

A. Fasano, BMJ. 2009;339:b3032
What is the best Strategy to Look for CD Subjects?

• General Screening?
• Case Findings (At Risk Groups)?

Detection of Celiac Disease in Primary Care: A Multicenter Case-Finding Study in North America

Efficacy of CD Case-Finding in Primary Care in North America

In only 1 year of case-finding intervention, the diagnosis of CD in a primary care setting increased by 43 folds
Detection of Celiac Disease in Primary Care: A Multicenter Case-Finding Study in North America: Cost Analysis

- **Screening Protocol Used:** TGB to all enrolled patients.
- **If positive or IgA deficient:** EMA.
- **2,568 patients interviewed.**
- **976 eligible and enrolled.**
- **Symptomatics, 1st and 2nd degree Relatives.**
- **Screening:**
  - TGB IgA Ab
  - EMA on positives TGB IgA.

**Cost Analysis:**
- **Total IgA tTG-IgA < 0.5 AU:**
  - Total IgA: $127,856
  - Negative tTG-IgA: 843
    - Cost: $4,841
  - Positive tTG-IgA:
    - EMA Negative: 954
      - Cost: $847
    - EMA Positive: 22
      - Cost: $2,328

**Cost per Positive Subject:** $6,176


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Trend of Celiac Disease Diagnosis in USA Since the CFCR 2003 Epidemiology Study

Since the CFCR epidemiology study published in 2003 the diagnosis of CD doubled approximately every 3 years. Currently ~150,000 of the projected 3,000,000 subjects affected by CD have been diagnosed.

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Increased Prevalence Over Time in U.S.A. (in Line with Other Autoimmune Diseases)

During the past 35 years the true prevalence of CD in USA doubled every 15 years.

C. Catassi et al, in press
Diagnostic principles

- Confirm diagnosis before treating
  - Diagnosis of Celiac Disease mandates a strict gluten-free diet for life
  - Following the diet is not easy
- QOL implications
- Failure to treat has potential long term adverse health consequences
  - Increased morbidity and mortality

Serological Test Comparison

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA-IgG</td>
<td>69 – 85</td>
<td>73 – 90</td>
</tr>
<tr>
<td>AGA-IgA</td>
<td>75 – 90</td>
<td>82 – 95</td>
</tr>
<tr>
<td>EMA (IgA)</td>
<td>85 – 98</td>
<td>97 – 100</td>
</tr>
<tr>
<td>TTG (IgA)</td>
<td>90 – 98</td>
<td>94 – 97</td>
</tr>
</tbody>
</table>


Endoscopic Findings

- Normal Appearing
- Scalloping
- Nodularity

Scallopind arrow pointing up.
Histological Features

Normal 0  
Infiltrative 1  
Hyperplastic 2  
Partial atrophy 3a  
Subtotal atrophy 3b  
Total atrophy 3c


**The 4 out of 5 Signs Rule**

1. Presence of signs or symptoms compatible with CD;
2. Positive serology (TTG +/- EMA);
3. Compatible HLA (DQ2 e/o DQ8 positive);
4. Positive intestinal biopsy (enteropathy typical of CD);
5. Resolution of symptoms following implementation of a gluten free diet
**Diagnosis: The Future to Come**

- Diagnostic algorithms to avoid intestinal biopsy;
- Biomarkers to predict onset of celiac disease in genetically susceptible individuals;
- Host-intestinal microbiome interaction;
- Pharmacometabonomics.

**Treatment**

- Only treatment for celiac disease is a gluten-free diet (GFD)
  - Strict, lifelong diet
  - Avoid:
    - Wheat
    - Rye
    - Barley

**Proline Prolyl Endopeptidases**

**Zonulin Inhibitor**

**CCR9 Inhibitor**

**Peptide-Based Vaccine**

Depiction of the intestinal mucosa with emphasis on the factors involved in the development of celiac disease in individuals with HLA-DQ2/DQ8 positive.
Prevention

HLA DQ2/DQ8 negative  STOP
At birth or at recruitment
HLA DQ2/DQ8 positive

Gluten introduction N=678
Group A N=345
Group B N=333

Stool C  Celiac S  IPT  Zonulin
6 months
12 months
18 months
24 months
30 months
36 months

Phone call

Age at Gluten Introduction and Risk of CD Development

% developing CD

months

0 10 20 30 40

0 2 4 6 8 10

gluten at 6 m

gluten at 12 m