Celiac Disease: The Past and The Present

The Center for Celiac Research and Mucosal Biology Research Center
University of Maryland School of Medicine
Baltimore, Maryland, U.S.A.
Celiac Disease Roadmap: Where we are coming from? Where are we going?

Years
2.5 M
The Human race appears on the face of hearth

Diet
Fruits, nuts, tubers
Occasional meat

Gluten as cause of CD
61 S. Gee
2,000 First description of CD
10,000 Change from nomadic to settled life style

Gluten free products
Advent of agriculture
Development of gluten containing grains
1
Cereals domestication started 10,000 years ago in the Fertile Crescent…

2
Catalhuyuc, The first town in the world was built 9,000 y ago

3
Agriculture slowly spread with a East–West gradient (1 Km/y)…

4
CD genes confer disadvantage in areas of high cereal consumption

INVERSE RELATIONSHIP BETWEEN CD FREQUENCY AND LENGTH OF TIME SINCE THE INTRODUCTION OF AGRICULTURE?
On the Coeliac Affection

There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children between one and five years old....

Signs of the disease are yielded by the faeces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for...

The causes of the disease are obscure. Children who suffer from it are not all weak in constitution. Errors in diet may perhaps be a cause, but what error? Why, out of a family of children all brought up in much the same way, should one alone suffer?

To regulate the food is the main part of treatment.... The allowance of farinaceous food must be small; highly starchy food, rice, sago, corn-flour are unfit. Malted food is better, also rusks or bread cut thin and well toasted on both sides....

The Banana Babies

WK Dicke, 1905 – 1962

1st case of CD at UMB: 1938
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
Normal small bowel

Gluten

Gluten-free diet

Celiac disease
Pathogenesis
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.
The Grass Family – (GRAMINEAE)

**Subfamily**
- Festucoideae

**Tribe**
- Zizaneae
- Festuceae
- Oryzeae
- Chlorideae
- Hordeae
- Aveneae

- wild rice
- rice
- wheat
- rye
- barley
- oat
- finger millet
  - (ragi)
The Celiac Iceberg

- Symptomatic Celiac Disease
- Silent Celiac Disease
- Latent Celiac Disease

Genetic susceptibility: DQ2, DQ8
Positive serology

Manifest mucosal lesion
Normal mucosa
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.
The Clinical Manifestations of Celiac Disease are More Heterogeneous Than Previously Appreciated: The North American Paradox

Celiac Disease — How to Handle a Clinical Chameleon

Alessio Fasano, M.D.

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten-containing grains (including wheat, rye, and barley) in genetically susceptible persons. The disease is associated with a high prevalence of autoimmunity and an increased risk of development of diabetes mellitus, and various lymphoma.

Epidemiologic studies conducted during the past decade, using specific and sensitive serologic tests, have revealed that celiac disease is one of the most common lifelong disorders in both Europe and the United States.
What Happened During the past 15 years?

The Recent CD Past History Seen Through the Center For Celiac Research

www.celiaccenter.org

1. Established in 1996
2. Multidisciplinary operation
3. Engaged in both basic science and clinical/translational research
4. Unique point of referral for CD patients (both pediatrics and adults) in USA.
5. **Paramount goal:** To increase the quality of life of CD patients and their families
How to achieve the paramount mission of the CFCR?

1. Implement the diagnosis to minimize errors and discomfort
2. Establish the dimension of the problem in North America
3. Increase the awareness of the disease
4. Create a network to work together toward specific goals
5. Implement the food labeling policy
6. Research and development
The Evolution of CD Serological Tests

...The availability of sensitive serological markers made it possible to discover CD even when the clinical suspicion was low.....
**Diagnosis**

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>
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<tbody>
<tr>
<td>AGA–IgG</td>
<td>69 – 85</td>
<td>73 – 90</td>
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<tr>
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<td>EMA (IgA)</td>
<td>85 – 98</td>
<td>97 – 100</td>
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<tr>
<td>TTG (IgA)</td>
<td>90 – 98</td>
<td>94 – 97</td>
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HLA Tests

HLA alleles associated with Celiac Disease
- DQ2 found in 95% of celiac patients
- DQ8 found in remaining patients
- DQ2 found in ~30% of general population

Value of HLA testing
- High negative predictive value
  - Negativity for DQ2/DQ8 excludes diagnosis of Celiac Disease with 99% confidence

Schuppan. Gastroenterology 2000;119:234
Kaukinen. Am J Gastroenterol 2002;97:695
HLA Tests

- Potential role for DQ2/DQ8
  - asymptomatic relatives
  - Down, Turner & Williams syndrome
  - type 1 diabetes
  - diagnostic dilemmas
Endoscopic Findings

Conventional endoscopy

Videocapsule Endoscopy
Histological Features

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

*Horvath K. Recent Advances in Pediatrics, 2002.*
How to achieve the paramount mission of the CFCR?

1. Implement the diagnostic tools to minimize errors
2. Establish the dimension of the problem in North America
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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
Risk Factors

The Genes

The Grains
Celiac Disease Epidemiological Study in USA

Population screened 13145

Healthy Individuals 4126
- Positive 31
  - Prevalence 1:133
- Negative 4095

Risk Groups 9019

Symptomatic subjects 3236
- Positive 81
  - Prevalence 1:40
- Negative 3155

1st degree relatives 4508
- Positive 205
  - Prevalence 1:22
- Negative 4303

2nd degree relatives 1275
- Positive 33
  - Prevalence 1:39
- Negative 1242

Projected number of celiacs in the U.S.A.: 2,115,954
Actual number of known celiacs in the U.S.A.: 40,000
For each known celiac there are 53 undiagnosed patients.

Where we go from here?

• Search for the other 2,091,212 CD Patients
What is the best Strategy to Look for CD Subjects?

• General Screening?
• Case Findings?
Case Finding Study

![Bar chart showing reasons for screening for different conditions.

Conditions listed from highest to lowest percentage: Bloating, Chronic fatigue, IBS, Constipation, RAP, Thyroid disease, Iron deficiency, Chronic diarrhea, Osteoporosis, Anemia, Reumatoid arthritis, Family history of CD, T1D, Psoriasis, Other AD, Weight loss, Neurological disorders.](image-url)
Prevalence of CD (and 95% CI) in selected at–risk subgroup of investigated patients. The dotted area is the prevalence of CD in the general U.S. population (2).

Case Finding Study

• The level of awareness of the disease among health-care professional is still low. Therefore, the disease remains highly under-diagnosed in North America.

• Our studies showed that our active case-finding strategy increased the rate of diagnosis by primary care physicians by 32-to 43-fold.

• Patients experiencing both intestinal symptoms (diarrhea, irritable bowel syndrome, constipation, and bloating) and extraintestinal symptoms (thyroid diseases, iron deficient anemia, osteoporosis) are at higher risk for CD compared with the general population.

• Our results have implications that may resolve in better patient care, a more cost-effective approach to the diagnosis of CD, and greater awareness among health-care professionals.
How to achieve the paramount mission of the CFCR?

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6. Research and development
CFCR initiatives to increase the awareness of celiac disease in the North America

1. International Walk for Celiac Disease;
2. Capitalization on the epidemiology study for PR coverage
3. Aggressive educational campaign for HCP;
4. High profile speak person (Rich Gannon)
5. Local and national coverage on newspapers (Wall Street Journal, Washington Post) and TV networks (Today Show).
CFCR initiatives to increase the awareness of celiac disease in the North America:

The educational initiatives

1. 9th International Symposium on Celiac Disease (2000);
2. NIH Consensus Conference (June 2004);
3. CDHNF initiative for CD national campaign (2004);
4. NASPGHAN CD Guidelines (2005);
5. State of the Art Lecture at the World Congress of Gastroenterology, Montreal Sept 11-14, 2005;
6. State of the Art Lecture at the NASPGHAN Annual Meeting (Oct 2005) where CD has been named the “Disease of the Year”;
Pediatric Gastroenterologists Launch New Campaign on Celiac Disease
Campaign Addresses Key Recommendation of National Institutes of Health Consensus Panel on Celiac Disease

Washington, DC; June 30, 2004 – The Children’s Digestive Health and Nutrition Foundation (CDHNF) with the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) today announced the launch of a new educational campaign on celiac disease, one of the most common genetic digestive conditions possibly affecting as many as three million Americans (up to 1%). This announcement comes immediately after a panel of leading medical experts reached a consensus that there is a significant need for increased education of physicians, dietitians and the public about celiac disease.

Convened in Washington, DC, the National Institutes of Health Consensus Development Conference on Celiac Disease involved the participation of 32 world renowned speakers and panelists along with more than 300 attendees who reviewed and discussed the latest scientific information on the disease. The findings show that a major problem concerning celiac disease is the under-recognition and lack of diagnosis, and therefore, lack of management of the disease leading to long-term consequences such as intestinal malignancies, osteoporosis, and infertility. Five members of the CDHNF scientific advisory board presented data and the President and President-Elect of NASPGHAN served as panel members.
**Campaign Leadership**

Alessio Fasano, MD, Chair  
CDHNF Celiac Disease Educational Campaign

Slide Set Task Force  
Carlo Catassi, MD

Richard Colletti, MD  
Martha Dirks, MD  
Stefano Guandalini, MD  
Janet Harnsberger, MD  
Ivor Hill, MD  
Edward Hoffenberg, MD  
Karoly Horvath, MD  
Alan Leichtner, MD  
Joseph Levy, MD  
Michelle Pietrzak, MD
Diagnosis and Treatment of Celiac Disease in Children

Clinical Practice Guideline Summary

PURPOSE:

This clinical practice guideline summary was developed to assist the primary and specialist medical provider in the diagnosis and treatment of celiac disease in children. Recommendations are based on an integration of a comprehensive and systematic review of the medical literature combined with expert opinion.

The following sections summarize the conclusions and recommendations of the NASPGHAN Celiac Disease Guideline Committee on the value of diagnostic tests and treatment modalities commonly used for the management of celiac disease, and how those strategies can be applied to clinical situations. The complete guideline
How to achieve the paramount mission of the CFCR?

1. Implement the diagnostic tools to minimize errors
2. Establish the dimension of the problem in the U.S.A.
3. Increase the awareness of the disease
4. Create a network to achieve specific goals (ACDA)
5. Implement the food labeling policy
6. Research and development

The dose–effect response (typical CD cases)
Gluten Treshold in GF food

*IT TAKES TWO TO TANGO!*

- The daily gluten intake is the product of gluten ppm in food and daily intake of wheat substitutes.
- Then the decision on the gluten threshold in GF food must take into account the variable intake of wheat substitutes.
Intake of gluten–free products in Europe

Gibert A et al, EJGH 2006
Tolerable daily intake of gluten and ppm of gluten in food for celiacs

<table>
<thead>
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<th>50 g</th>
<th>100 g</th>
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<td>20 ppm</td>
<td>1 mg</td>
<td>2 mg</td>
<td>4 mg</td>
<td>6 mg</td>
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Toward a safe gluten threshold

WHERE DO WE STAND NOW?

risk area
Toward a safe gluten threshold
A PRUDENT VIEW

wheat substitutes (g x day)

safe area
grey area
risk area
Key Questions About the Double Threshold Proposed by Codex

• Is there an advantage in terms of availability of products?
• Is there an advantage in terms of palatability?
• Is there an advantage in terms of economics?

If the answer is no to any of these questions, why risking?
WASHINGTON – The Food and Drug Administration recommended new standards for a fast-growing sector of the food industry: products that lack a protein called gluten, which is found in grains such as wheat and barley and can trigger an autoimmune reaction that attacks the small intestine.

In a proposal published online yesterday, the agency said companies may label foods “gluten-free” if they don’t contain wheat, barley, rye or their hybrids, or if they contain fewer than 20 parts per million gluten. Currently, some companies use the label to describe products that are naturally gluten-free, such as fruits or meat. Under ...
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Celiac Disease: The Future
To Be Continued.........