Celiac Disease
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Advisory Committee/Board Member: Alvine, Inc.
Consultant: Flamentera, Ironwood, Inc, Nexpep, Shire
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What is Celiac Disease?

- It is a inflammatory state of the small intestine that occurs in genetically predisposed individuals and resolves with exclusion of dietary gluten.
Evolutionary Collision

Wheat

Human Immune System

Kasorda, 1992
Pathogenesis of Celiac Disease

- Genetics
- Environment

Immune response

Inflammation
Genetics of Celiac Disease

- Strong family predisposition
  Monozygous twins (80%), siblings (10%) kids (5-10%)

- HLA association DQ2 and DQ8 required but not sufficient

- Non HLA genes suspected but not confirmed

- Down’s Turner’s and William’s syndrome
Gluten Is The Seed Storage Protein In Wheat, Rye, Barley, And Triticale

Certain grassy weeds also contain gluten.
Pathogenesis

Genetics

Gluten

Necessary Causes

Gender
Infant feeding
Infections
Others

Risk Factors

Pathogenesis

Celiac disease
The Swedish Epidemic
Swedish Epidemic

- Delayed gluten introduction from 4 to 6 months of age
- Weaning finished before cereals started
- Increased gluten in baby foods > 6 months of age

Epilogue: the rate of celiac in the epidemic cohort is now 3% at age of 12!
Typical Celiac Disease
Steatorrhea

This also happens with liver disease
The “Old” Disease

- A rare disorder typical of infancy
- Everyone had diarrhea/steatorrhea
- Wide incidence fluctuations in space (1/400 Ireland to 1/10,000 Denmark) and in time
- A disease of essentially European origin
- That was rare in North America

Talley, AJG, 1994
Presentations of Celiac Disease

• Classic malabsorptive syndrome (25%)
  diarrhea, steatorrhea, weight loss, multiple deficiencies

• Monosymptomatic (50%)
  Anemia, diarrhea, lactose intolerance, constipation

• Acute Abdomen (rare)
  abdominal pain, intussception, vomiting, obstruction perforation, lymphoma

• Non-GI presentations (25%)
  Infertility, bone disease, neurological disease, short stature, brittle diabetes, chronic fatigue, abnormal LFTS
Dermatitis Herpetiformis

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

Osteoporosis/Osteomalacia

Low bone mineral density improves on a gluten-free diet. In fact it will not improve without it!
Recurrent Aphthous Stomatitis
Fe-Deficient Anemia Resistant to Oral Fe

- Most common non-GI manifestation in some studies
  - Murray, CGH, 2003

- 5-8% of adults with unexplained iron deficiency anemia have Celiac Disease

- 5-15% of patients undergoing endoscopy for iron deficiency anemia have celiac disease
  - Vogelsang, 98; Grisolano, 2004

- 30-50% of patients getting EGD for anemia do not get duodenal biopsies!
  - Harewood, 2005
Celiac Disease: Acute Abdomen

- Mimic partial small bowel obstruction
- Perforation
- Stricture
- Lymphoma
- Intussusception
Abnormal Liver Blood Tests

• Incidental elevated serum transaminases (ALT, AST)
  • Up to 9% may have silent Celiac Disease
  • Liver biopsies in these patients showed non-specific reactive hepatitis
  • Liver enzymes normalize on gluten-free diet

• Occasionally severe liver disease

Rubio-Tapia et al. Liver international, 2008
Rubio-Tapia and Murray, Hepatology, 2007
Celiac Disease and other liver diseases

- PBC    2-10%
- PSC    case reports
- PSC in prior dx of CD    HR 4.4
- AIH    variable    3-8%
- Hep C    2% (may be triggered by interferon treatment)
- No increased risk of transplantation
Who Gets Celiac Disease?

- Adults >> children, female > males
- Worldwide, mostly Caucasians
- Any age including elderly
- People with other immune disorders
  - Type one diabetes mellitus
  - Sjogren’s syndrome
  - Thyroid disease
  - Lupus, Addison’s disease
- Family members of celiacs
The Celiac Iceberg

Symptomatic Celiac Disease

Silent Celiac Disease

Latent Celiac Disease

Manifest mucosal lesion

Normal Mucosa

Genetic susceptibility: - DQ2, DQ8
Positive serology

1:133
World Map Indicating Prevalence of Celiac Disease

~1%  1-2%  >2%  <0.5%  Report of cases  N/A

How Do You Find It?

Diagnostic Tests
Diagnostic Criteria

- Villous atrophy with chronic inflammation in the proximal small intestine while eating gluten
- Objective clinical response to a gluten free diet
- Serology provides supportive evidence

ESPHGAN Guidelines 1991
UEDW Guidelines 2001
Serologic Tests In CD Diagnosis

- Anti endomysial antibodies (EMA)
  - Indirect immunofluorescence
  - Excellent specificity and good sensitivity
  - Expensive (monkey esophagus needed)
  - Subjective

- Anti whole Gliadin antibodies (AGA)
  - Cheap
  - Easy
  - Fair sensitivity and poor specificity

New deaminated Gliadin peptide antibodies

- Tissue transglutaminase antibodies (TTG)
  - Good sensitivity and specificity
  - Easy to test
Limitations of Serology

- IgA deficiency (3-5% of celiacs are IgA deficient and 10% of IgA deficient patients have CD)
- Less sensitive for partial villous atrophy
- Effect of prior gluten free diet

Rostami, 1999
Histopathology of Celiac Disease

How good are biopsies?
Histological Features Vary

False Positive Biopsies

- Poorly oriented “flattened biopsies”
- NSAIDS
- Self-limited enteritis in 7 adults Goldstein, Am J Clin Path 2004
- Tropical sprue (travel history)
- Combined variable immunoglobulin deficiency
- Autoimmune enteropathy Akram et al. CGH 2007
- Non granulomatous enterocolitis
What About Patients on GFD Diet?

- Often unhappy patient
- Serology and biopsies can normalize
- HLA type might help
- Challenge
- Some patients will not eat gluten
- Why argue with success if diet is nutritionally adequate?
Genetic Testing for Celiac disease

- Used DNA methods to HLA type
- Detects pairs of genes
- Good to rule out if absent
- Not specific
- Direct to patient testing
Celiac Disease And HLA Risk
When to Use HLA?

- People on a gluten free diet (including refractory)
- Seronegative positive biopsy patients
- Those at genetic risk who are seronegative
  - Down’s Syndrome
  - Turner’s syndrome
  - William’s syndrome
  - Asymptomatic family members
  - Type one diabetes

Usual prevalence of DQ2

High prevalence of DQ2/8
The Case for Screening

• ~ 1% of general population
• Long pre-symptomatic phase
• Diverse symptoms/groups affected
• Increased risk of malignancy
• Easily applied detection test
• Treatable
• Big unknown is natural history
The Silence of the Intestines: Increased Prevalence and Mortality of Undiagnosed Celiac Disease


Mayo Clinic Rochester
Subjects: 50-year Old Sera

- The sera was collected from 1948-1954 in 8916 healthy persons*

(Warren Airforce Base Cohort - WAFB)

<table>
<thead>
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<th>Age (mean ± SD)</th>
<th>20.5 ± 2.8</th>
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<tbody>
<tr>
<td>Gender</td>
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<tr>
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<td>99%</td>
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<tr>
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<tr>
<td>WHITE</td>
<td>89.1%</td>
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<tr>
<td>African American</td>
<td>10.5%</td>
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<tr>
<td>Others</td>
<td>0.4%</td>
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</tbody>
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* Denny FW, et al. Prevention…streptococcic infection. JAMA 1950
Survival

Survival (%)

Time since serum draw (years)

Mortality
HR = 3.8 (1.9, 7.2)
P<0.001

Negatives (76%)
Positives (36%)
Management Plan

• Explain the disease
• Strongly advocate a gluten free diet
• Refer to expert dietitian!
• Check bone density
• Identify and treat deficiencies
• Calcium and vitamin D replacement
• Support group
Summary

• Celiac Disease is common ~1%
• It can present in many ways or remain covert
• Frequent in the endoscopy suite
• Detected by serology (tTg-IgA)
• Confirmed by biopsy
• Treatment is dietary ……
Crowds panic as flooding threatens Ireland...