IT TAKES A VILLUS....

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Nothing to disclose
Objectives

- Better understanding pathogenesis celiac disease
- Better understanding of available screening tests
- Better understanding of diagnosis: DO NOT START GFD until diagnosis
- New perspectives in treatment
clarification

- Wheat allergy
- CELIAC DISEASE
- Non-celiac gluten sensitivity
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

- Genetic predisposition
- Environmental triggers
  - Dietary
  - Non dietary?
Pathogenesis

Genetics

Gluten

Necessary Causes

Gender
Infant feeding
Infections
Others

Risk Factors

Celiac disease

Pathogenesis?
Genetics

- Strong HLA association
- 90 - 95% of patients HLA-DQ2 – also found in 20 - 30% of controls
  - Most of the remainder are HLA - DQ8
- 10% of patients have an affected first degree relative
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
  - Chlorideae
    - wild rice
- Oryzeae
  - rice
- Hordeae
  - wheat
  - rye
  - barley
- Aveneae
  - oat
- Festucceae
  - finger millet (ragi)
- Oryzeae
  - rice
- Hordeae
  - wheat
- Aveneae
  - oat
- Festucceae
  - finger millet (ragi)
- Oryzeae
  - rice
- Hordeae
  - wheat
- Aveneae
  - oat
- Festucceae
  - finger millet (ragi)
Dietary Factors

- 33 amino acid peptide in gliadin contains critical epitopes – high in glutamine and proline
- Resistant to digestion in lumen
- Penetrates epithelial barrier
- Modified by the enzyme tissue transglutaminase – deamidates glutamine residues to glutamic acid
- Resulting higher affinity binding to HLA DQ2 molecule on the surface of antigen-presenting cells
Non-Dietary Factors

- Infections
  - Viral infections
  - Parasitic infestations
- Other?
Tissue Transglutaminase (TTG)

- Normal gut enzyme released during injury and stabilizes the cross-linking of proteins in granulation tissue
- Role in Celiac Disease
  - Modification of gliadin epitopes
  - Autoantibodies against TTG correlate with active Celiac Disease - ? involved in pathogenesis
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 Celiac Disease Were Found Among:

- Relatives
  - Patients with short stature, anemia, fatigue, hypertransaminasemia
  - Autoimmune disorders, Down’s, IgA deficiency, neuropathies, osteoporosis, infertility

- Associated diseases

- “Healthy” groups
  - Blood donors, students, general population
The Size of the Submerged Iceberg is Decreasing in Many Countries Due to Active Case-Finding

Even an intensive policy of Celiac Disease case-finding will leave at least 50% of celiacs without a diagnosis.
Natural History Of Celiac Disease At Glance

**ENVIRONMENTAL TRIGGERS**
- Gluten "load"
- Intestinal infections
- Pregnancy
- Cancer

**THE PROPORTION OF SYMPTOMATIC CASES INCREASES WITH AGE**

- Genetically predisposed subject
- Development of celiac enteropathy
- Clinically overt CD
- Silent CD
- Persistently Silent CD
- CD complications
- Persistently silent CD

**THE PROPORTION OF SYMPTOMATIC CASES INCREASES WITH AGE**
Clinical Manifestations

- Gastrointestinal ("classical")
- Non-gastrointestinal ("atypical")
- Asymptomatic

In addition, Celiac Disease may be associated with other conditions, and mostly with:
  - Autoimmune disorders
  - Some syndromes
The Celiac Iceberg

Symptomatic Celiac Disease

Silent Celiac Disease

Potential Celiac Disease

Manifest mucosal lesion

Normal Mucosa

Genetic susceptibility: - DQ2, DQ8
Positive serology
Typical Celiac Disease
Gastrointestinal Manifestations ("Classic")

Most common age of presentation: 6-24 months

- Chronic or recurrent diarrhea
- Abdominal distension
- Anorexia
- Failure to thrive or weight loss

Rarely: Celiac crisis

- Abdominal pain
- Vomiting
- Constipation
- Irritability
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
Dermatitis Herpetiformis

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

Dental Enamel Defects

Involve the secondary dentition
May be the only presenting sign of Celiac Disease
Low bone mineral density improves in children on a gluten-free diet.
Celiac Disease Complicated by Enteropathy-Associated T-cell Lymphoma (EATL)

By permission of G. Holmes, Derby (UK)
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
Fe-Deficient Anemia
Resistant to Oral Fe

- Most common non-GI manifestation in some adult studies
- 5-8% of adults with unexplained iron deficiency anemia have Celiac Disease
- In children with newly diagnosed Celiac Disease:
  - Anemia is common
  - Little evidence that Celiac Disease is common in children presenting with anemia
Hepatitis

- Some evidence for elevated serum transaminases (ALT, AST) in adults with untreated Celiac Disease
  - Up to 9% of adults with elevated ALT, AST may have silent Celiac Disease
  - Liver biopsies in these patients showed non-specific reactive hepatitis
  - Liver enzymes normalized on gluten-free diet
Arthritis and Neurological Problems

- **Arthritis in adults**
  - Fairly common, including those on gluten-free diets
- **Juvenile chronic arthritis**
  - Up to 3% have Celiac Disease
- **Neurological problems**
  - Epilepsy with cranial calcifications in adults
  - Evidence for this condition in children with Celiac Disease is not as strong
### 3 – Asymptomatic

#### Silent

- **Silent:**
  - No or minimal symptoms, “damaged” mucosa and positive serology

Identified by screening asymptomatic individuals from groups at risk such:

- First degree relatives
- Down syndrome patients
- Type 1 diabetes patients, etc.
3 – Asymptomatic

Silent

Potential

- Potential: No symptoms, normal mucosa
  
  - May show positive serology. Identified by following in time asymptomatic individuals previously identified at screening from groups at risk. These individuals, given the “right” circumstances, will develop at some point in time mucosal changes (± symptoms)
Asymptomatic patients are still at risk of osteopenia/osteoporosis. Treatment with a gluten-free diet is recommended for asymptomatic children with proven intestinal changes of Celiac Disease who have:

- type 1 diabetes
- selective IgA deficiency
- Down syndrome
- Turner syndrome
- Williams syndrome
- autoimmune thyroiditis
- a first degree relative with Celiac Disease
Associated Conditions

The prevalence of Celiac Disease is higher in patients who have the following:

- Certain genetic disorders or syndromes
- Other autoimmune conditions
- Relative of a biopsy-proven celiac
Genetic Disorders

- Down Syndrome: 4-19%
- Turner Syndrome: 4-8%
- Williams Syndrome: 8.2%
- IgA Deficiency: 7%
  - Can complicate serologic screening
Prevalence of Celiac Disease is Higher in Other Autoimmune Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes Mellitus</td>
<td>3.5 - 10%</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>4 - 8%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.5 - 7.5%</td>
</tr>
<tr>
<td>Autoimmune liver diseases</td>
<td>6 - 8%</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>2 - 15%</td>
</tr>
<tr>
<td>Idiopathic dilated cardiomyopathy</td>
<td>5.7%</td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>3.6%</td>
</tr>
</tbody>
</table>
Relatives

- Healthy population: 1:133
- 1st degree relatives: 1:18 to 1:22
- 2nd degree relatives: 1:24 to 1:39

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
Diagnosis

- Diagnosis of Celiac Disease requires:
  - characteristic small intestinal histology in a symptomatic child
  - complete symptom resolution on gluten-free diet
- Serological tests may support diagnosis
- Select cases may need additional diagnostic testing

ESPGHAN working group. Arch Dis Child 1990;65:909
Serological Tests

Role of serological tests:
- Identify symptomatic individuals who need a biopsy
- Screening of asymptomatic “at risk” individuals
- Supportive evidence for the diagnosis
- Monitoring dietary compliance
Serological testing

- Total IgA
- IgA Tissue Transglutaminase (TTG)
- IgA Anti-endomysial Antibody (EMA)
- IgG Deamidated gliadin peptides (DGP)
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
Endoscopic Findings

- Normal Appearing
- Scalloping
- Nodularity
Biopsy Diagnosis

- Histologic Features:
  - Increased IEL’s ( > 30/100 enterocytes)
  - Loss of nuclear polarity
  - Change from columnar to cuboid
  - Lamina propria cellular infiltrate
  - Crypt elongation and hyperplasia
  - Increased crypt mitotic index
  - Progressive villous flattening
Patterns of Mucosal Immunopathology

Type 0
Normal
Celiac Disease (latent)

Type 1
Infiltrative
Celiac
Giardiasis
Milk intolerance
Tropical sprue
Marasmus
GVHR

Type 2
Hyperplastic
Celiac
Giardiasis
Milk intolerance
Tropical sprue
Marasmus
GVHR

Type 3
Flat destructive
Celiac
Giardiasis
Milk intolerance
Tropical sprue
Marasmus
GVHR

Histological Features

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

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

- You can have a positive outlook
- Learning to live:
  - Gluten-free foods are better tasting than ever before
  - The diet gets easier as patients adjust to it
  - It is not necessary to restrict the patient’s lifestyle, it is just a different way of eating
- Don’t make it harder than it needs to be
  - Why following a strict gluten-free diet is vital to living a full, healthy life
- Weight management may become a concern
Dietary Adherence: A Common Problem

- Only 50% of Americans with a chronic illness adhere to their treatment regimen including:
  - diet
  - exercise
  - medication

- Dietary compliance can be the most difficult aspect of treatment
Health Beliefs of Adults with Celiac Disease

- Survey of 100 people in Celiac Disease support group (Buffalo, NY)
  - Number of people who agreed with following statements:
    - “If I eat less gluten I will have less intestinal damage.” —51%
    - “I’ve lived this long eating gluten, how much will the gluten-free diet really help me now?” —33%
    - “My doctor should be the one to tell me when I need follow up testing.” —26%
    - “Scientist/doctors still haven’t proven that gluten really hurts them.” —16%
Internal Adherence Factors Include:

- Knowledge about the gluten-free diet
- Understanding the risk factors and serious complications can occur to the patient
- Ability to break down big changes into smaller steps
  - Ability to simplify or make behavior routine
- Ability to reinforce positive changes internally
- Positive coping skills
- Ability to recognize and manage mental health issues
- Trust in physicians and dietitians
The Key to Dietary Compliance is Follow Up Care

- NASPGHAN Guidelines apply to adults and children
- The health effects are motivation
  - When one believes they are real
  - Testing measures the health effects of eating gluten
- Follow up testing provides important feedback
The Key to Dietary Compliance is Follow Up Care

- Test results are a powerful motivator
  - especially those who do not have symptoms when they eat gluten
- Patients/parents look to the physician to tell them when follow-up testing is needed
  - Proactive follow-up measures can reinforce adherence
Celiac Disease-Diagnosis: The Future

- Diagnosis Strategies
  - Mass population screening
    - Not cost effective (research tool)
    - Benefits uncertain
  - Active case finding
    - Selective serological testing
    - Biopsy confirmation
Celiac Disease-Diagnosis: The Future

- Non biopsy diagnosis
  - Characteristic clinical subgroups
  - Refined (standardized) serological tests
  - Use of HLA typing
  - Discovery of biomarkers
  - Specific gene identification
Celiac Disease-Management: The Future

- Gluten free diet remains best treatment
- Refined understanding of “gluten free”
- FDA mandates better food labeling
- Commercial recognition of the “value” of gluten free products
CD Drug Development

- Intraluminal therapies
  - ALV003
  - Lazarotide
  - BL-7010

- Immunosuppressants
  - CCX282-B
  - Hu-Mik-Beta-1

- Immunotherapies
  - Nexvax-2
  - COUR-NP-GLI
THANK YOU : it is not as easy as it looks!!!

QUESTIONS?
“Oh, yes...Mr. Celiac disease. I'm terrible with faces but I never forget a bowel biopsy.”