Celiac Disease: Where are we in 2015?

Peggy Marcon
Hospital for Sick Children
October 2015
Conflicts

• None except I eat gluten.

• And I will not be talking about non-Celiac gluten sensitivity!
Goals

1. Who to screen and what test to use
2. Role of small bowel biopsy
3. Long-term follow up
4. Long-term morbidity and mortality
What is Celiac Disease

- Celiac disease is an autoimmune condition
- Occurs in genetically susceptible individuals
  - DQ2 (90%) and/or DQ8 (7%) positive HLA haplotype is necessary but not sufficient
- A unique autoimmune disorder because:
  - both the ongoing environmental trigger (gluten) and the autoantigen (tissue Transglutaminase) are known
  - elimination of the environmental trigger leads to a complete resolution of the disease (in most people)
Celiac Disease in London, Year 1938
In 2015: The World!
Presentation of Childhood celiac disease

• 1990-1996
• 2 years old
• 2 / 100,000

• 2000-2006
• 9 years old
• 7.3 / 100,000

McGowan KE, Castiglione DA, Butzner JD
The Celiac Iceberg

Symptomatic Celiac Disease

Silent Celiac Disease

Latent Celiac Disease

Manifest mucosal lesion

Normal Mucosa

Genetic susceptibility: - DQ2, DQ8
Positive serology

# cases rising
When to screen?

- Anorexia
- *Failure to thrive or weight loss*
- *Slowed growth Velocity*
- *Short Stature / stunted growth*
- Abdominal pain
- Vomiting
- *Chronic or recurrent diarrhea*
- Constipation
- *Abdominal distension / bloating / Indigestion*
- Anemia *(Fe def or low B12)*
- Acid Reflux
- *Irritable Bowel Syndrome*
Non Gastrointestinal Manifestations

- Osteopenia/Osteoporosis/Fractures
- Short Stature
- Delayed Puberty
- Recurrent aphthous ulcers
- Hepatitis
- Arthritis
- Epilepsy with occipital calcifications
- Neurological Symptoms
- Autoimmune Disease
- Fertility issues

Dermatitis Herpetiformis

Dental enamel hypoplasia of permanent teeth
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>
<tr>
<td>? Schizophrenia</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Best Studied with largest numbers**
Genetic Disorders

- Trisomy 21 Syndrome: 4-19%
- Turner Syndrome: 4-8%
- Williams Syndrome: 8.2%
- IgA Deficiency: 7%
  - Can complicate serologic screening
  - DGA IgG not so specific!
And these genetics?

- Healthy population: 1:100
- 1st degree relatives: 1:18 to 1:22
- 2nd degree relatives: 1:24 to 1:39

“CD fulfills several WHO criteria for mass screening (high prevalence, available treatment and difficult clinical detection), but it has not yet been established that treatment of asymptomatic CD may reduce the excessive risk of severe complications, leading to higher QOL nor that it is cost-effective.”

What Test?

“standardized ELISA-based assays for IgA autoantibodies against tissue transglutaminase remain the test of choice for most populations”

*Am J Gastroenterol* 2010; 105:2520–2524; 
Update on Serologic Testing in Celiac Disease
Cost of screen?

<table>
<thead>
<tr>
<th>Order</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue Transglutaminase IgA Antibody (tTG)</td>
<td>$30.00</td>
</tr>
<tr>
<td>Endomysial Antibody (EMA)</td>
<td>$35.00</td>
</tr>
<tr>
<td>Celiac Panel (tTG-IgA and DGP IgG)</td>
<td>$55.00</td>
</tr>
<tr>
<td>Gliadin Panel (Gliadin IgA and IgG)</td>
<td>$66.00</td>
</tr>
<tr>
<td>Deamidated Gliadin Peptide IgG Ab (DGP)</td>
<td>$30.00</td>
</tr>
</tbody>
</table>

Add a serum IgA – it is covered and you do not need the more NON SPECIFIC DGP.
Point of Care Testing or From the Drugstore or On-Line

There are fairly reliable but the “at home” ones depend on the skill of the “technician”!

CELIAC DISEASE DNA TEST
$249 CAD, results in 7 to 14 days simple mouth swab

CDN $100

CDN $149.03
WHAT IF THEY ARE ALREADY GLUTEN FREE?
* Beware the IgG antibodies

Oxentenko & Murray, Clin Gastro Hepatol 2015;13:1396-1404
What to do with a positive screen?

• Gold Standard is a small bowel biopsy.
• Allows follow up biopsy if symptoms do not improve.
• May induce better compliance!

• 10% of children continue with symptoms after GFD
• Up to 50% of adults continue with symptoms after GFD
Small Bowel Biopsies

Normal

Untreated Celiac Disease
Child / Adolescent with Symptoms suggestive of CD

Anti-TG2 IgA & total IgA

Anti-TG2 positive

Anti-TG2 negative

Not CD

Consider further diagnostic testing if:
- IgA deficiency
- Age: < 2 years
- History: low gluten intake
- drug pretreatment
- severe symptoms
- associated diseases

Transfer to Paediatric GI
Paed. GI discusses with family the 2 diagnostic pathways and consequences considering patient’s history & anti-TG2 titer

Pos. Anti-TG2 > 10 x normal

Pos. Anti-TG2 < 10 x normal

Pos. Anti-TG2 > 10 x normal

Pos. Anti-TG2 < 10 x normal

EMA & HLA DQ8/DQ2

Not available

EMA & HLA DQ8/DQ2

Not available

OEGD & biopsies

Marsh 0-1

Marsh 2 or 3

Unclear case
Consider:
- false pos. serology
- false neg. biopsy or potential CD
- Extended evaluation of HLA/serology/biopsies

CD+

GFD & F/u

CD+

GFD & F/u
And No Biopsy?

- Are ESPGHAN “Biopsy Sparing” Guidelines for Celiac Disease also Suitable for Asymptomatic Patients?
  - Am J Gastroenterol 2015 Sep 15. [Epub ahead of print]

- 196 patients (68.53%) had anti-tTG titers ≥10 times ULN.
- 156/196 patients (79.59%) also had symptoms suggestive of CD ("high-titer" symptomatic);
  - 142 patients (91.02%) showed severe lesion degree (3a, 3b, 3c)
- 40/196 patients (20.40%) were asymptomatic ("high-titer" asymptomatic)
  - 37 patients (92.5%) of them showed severe lesion degree (3a, 3b, 3c)
- No difference in histological damage was found between "high-titer" symptomatic and "high-titer" asymptomatic children (Fisher exact test, P=1.000)
Current Treatment is a diet!

Phase 2 trials of other therapies are looking at those who don’t fully respond to a GFD.
Gluten

The Grass Family - (GRAMINEAE)

Subfamily
Festucoideae

Tribe
Zizaneae  Oryzeae  Hordeae  Aveneae  Festuceaea  Chlorideae
wild rice  rice  oat  finger millet (ragi)  teff

wheat  rye  barley
What to do with these?

• Many are asymptomatic
• Not clear of life long risks with “non-compliance”
• Could diet prevent morbidity / early mortality?

What – NO pizza!
Why should I GO on this diet?
Increased Overall Mortality In Adult Life

- AUTOIMMUNE DISEASES
- OSTEOPOROSIS
- LIVER DISEASES
- CANCER

**ORIGINAL INVESTIGATION**

Causes of Death in Patients With Celiac Disease in a Population-Based Swedish Cohort

- Uhrike Peters, PhD; Johan Askling, MD; Gloria Grudley, MS; Anna Fors Ekhom, MD, PhD; Martha Linnet, MD

Mortality in patients with coeliac disease and their relatives: a cohort study

- Giovanni Corazza, Gino Roberto Corazza, Vincenzo Bagnardi, Giovanna Brusco, Carolina Ciacci, Mario Cottone, Carla Sardina Guidetti, Paolo Usai, Pietro Cesari, Maria Antonietta Pelli, Silvano Lopertido, Umberto Voita, Antonino Calabrò, Maria Cerro, for the Club del Tenue Study Group
Reason to abstain?

- Risk of CD in other autoimmune disease always seems to run around the 5% mark.

- Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet.
  - 178 of 974 with Celiac Disease developed AID
  - 5.4 per 1000 patient-years during adherence
  - 11.3 per 1000 patient-years during non-adherence

  » Clin Gastroenterol Hepatol. 2008 Jul;6(7):753-8
Evidence that diagnosis makes other autoimmune diseases “better”.

- In general
  - “Improve” when Celiac Disease has symptoms
  - Provide better nutrition
- T1D
  - Insulin control improves only if you are symptomatic from your Celiac Disease.
  - New data suggesting maybe GFD compliance in T1D (symptomatic or asymptomatic) may decrease morbidity risks
- JRA
  - all had symptom improvement of JRA
- Not clear about other AIDs.
Affect on Mortality

USA

• US Airman
• Blooded collected 1948-54
• F/U 45 years
• 4-fold increase in mortality in UN-DIAGNOSED Celiac Disease

- *Mayo Clinic*

Finland

• N = 6987
• Blood collected 1978-80
• Sera run 2001
• 1% of population TTG
• Mortality no different from general population

Meta-Analysis

• Combined 17 studies
• Over-all increase in mortality
  - OR 1.24 (95%)

• Malignancy – NO overall increase in risk
  - ↑ Risk Non-Hodgkin Lymphoma OR 2.61
  - ↑ Risk T-Cell Non-Hodgkin Lymphoma 15.84
Potential Nutritional Complications in Untreated Celiac Disease

- Low Iron
- Low Folate
- Low Vitamin B-12
- Low Vitamins ADEK
- Low Thiamine
- Low Niacin
- Low B6 (rare)
- Low Beta-carotene
- Low Zinc
- Essential Fatty Acid Deficiency
What about my baby?

- Two large studies suggested timing of gluten exposure and breast feeding didn’t change the incidence at 5 years of age.
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
Follow up guidelines

• Rather wishy washy
• Say you should provide follow-up
• Better compliance
• Need more data on decreased morbidity
Celiac Guidelines and References

• Guideline for the Diagnosis and Treatment of Celiac Disease in Children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. (2005) @ NASPGHAN website

• See. Nat Rev Gastroenterol Hepatol Practical insights into gluten-free diets. 2015 Sep 22. [Epub ahead of print]

Resources

• DeMelo. Can J Diabetes Celiac Disease and Type 1 Diabetes in Adults: Is This a High-Risk Group for Screening 2015 Aug 17. [Epub ahead of print]
• Review of Gluten issues coming out in JPGN
• www.celiac.ca
• http://www.cdhf.ca
Resources

- Reputable websites
  - NASPGHAN
  - Celiac.Com (www.celiac.com)
  - National Institutes of Health (www.niddk.nih.gov)
  - American Dietetic Association (www.eatright.org)

- Local Support Groups
  - Celiac.Com (www.celiac.com)

- National Support Groups
  - The Gluten Intolerance Group – GIG (www.gluten.net)
  - Celiac Disease Foundation – CDF (www.celiac.org)

- Research and Information
  - Center for Celiac Research (www.celiaccenter.org)