Celiac disease: Review of immunology, diagnosis and epidemiology

D.ssa Renata Auricchio,
University Federico II, Naples, Italy
Aims
Celiac disease in the 2000s: what’s new?
New Diagnostic criteria and their criticisms.
Potential celiac disease: a model to study celiac disease pathogenesis
Is possible to prevent CD?
Celiac disease

• Coeliac disease is a lifelong intolerance to wheat gluten and related prolamines in rye and barley, resulting in intestinal lesion.

• It has become a common health problem in Western countries and most developing countries.

• The clinical picture is pleiomorphic and most cases go undiagnosed.
Celiac Disease
Interplay between genetic and environmental factors

Gluten proteins (in wheat, rye, barley)

Environmental factors

Genetic factors

Normal intestine → Gluten → Celiac disease

HLA-DQ2 gene on 6p21: ~40%

Gene 1
Gene 2
....
Gene n
Prevalence of CD: wheat consumption

Fig 1. World map of level of wheat consumption (g/person/day).
Data from the Food and Agriculture Organization of the United Nations database (http://www.fao.org).

Prevalence of CD: frequency of HLA DQ2

Fig. 2. World map of frequency of HLA-DQ2 (%). Data from the allelefrequencies.net database [12].

Prevalence of CD

Fig. 5. World map of celiac disease prevalence (%). Data from studies based on the screening of unselected samples [11,17–48]. Studies on blood donors were excluded because they differed from the general population in social, health-related, and gender variables.

Changing clinical features of CD in the last decades

Diarrhea in the youngest (<3 y), abdominal pain in the oldest. Less frequent than previous cohort failure to thrive and iron deficiency anemia.

Savilahti E, Acta Ped 2010;99:1026
CD patients in NY have abdominal pain and constipation and they are older (mean age 10.7 ± 4.3 y).

Khatib M, JPGN 2016;62 (1):60-63

Changing clinical features of CD in the last decades
Reduction of **weight velocity** could predict CD diagnosis before any other clinical and serological markers in at risk children

*Unpublished data*
Intestinal immune events may contribute to symptoms and complications

• Through production of cytokines and other inflammatory mediators (fatigue, weight loss, increased bone turnover)

• Favouring autoimmunity (increased intestinal permeability, enhancing mechanisms leading to induction of autoantibodies)

• Inducing local intestinal complications (e.g. lymphomagenic activity of IL15)
New Diagnostic criteria and their criticisms.
High serum anti-TG2 antibodies correlation with histology lesions in children

Table 1. The positive predictive value (PPV) for different cut-offs of IgA-tissue transglutaminase antibody (TGA) levels in 146 patients

<table>
<thead>
<tr>
<th>TGA* cut-off</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coeliac</td>
</tr>
<tr>
<td>&lt;10</td>
<td>95</td>
</tr>
<tr>
<td>10-30</td>
<td>10</td>
</tr>
<tr>
<td>&gt;30-50</td>
<td>16.7</td>
</tr>
<tr>
<td>&gt;50</td>
<td>&gt;33</td>
</tr>
<tr>
<td>&gt;100</td>
<td>100</td>
</tr>
</tbody>
</table>

* TGA is expressed as U/mL and as multiples of the upper limit of normal (ULN).

Dahlbom et al. JPGN, 2009

Hill, Aliment Pharm Ther 2008
**Results:** The ratio of the villous height to crypt depth correlated with the severity of gastrointestinal symptoms, quality-of-life scores, laboratory test results, numbers of intraepithelial CD3+ cells, and serum levels of antibodies associated with celiac disease.
Biopsy: recommendations

Histological assessment may be omitted in:

• Symptomatic cases
• With high IgA anti-TG2 levels, (10 x upper normal limits)
• Verified by EMA positivity
• HLA DQ2 and/or DQ8 heterodimer positive

Follow up should include significant symptomatic improvement as well as normalization of coeliac antibody tests.
Critical issues

What we mean for symptomatic children?

Anti TG2 kits performances are different
Should cut offs limits be validated locally?
Is it necessary an international standard for antiTG2 antibodies?
EMA are really necessary?

HLA typing really adds to serology in those with anti-TG2 >10xULN
How many false positive we have using the new criteria?

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>ESPGHAN criteria + ve</th>
<th>Villous atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donat (JPGN 2015)</td>
<td>751</td>
<td>336</td>
<td>336 (100)</td>
</tr>
<tr>
<td>Klapp (JPGN 2013)</td>
<td>50</td>
<td>116</td>
<td>116 (100)</td>
</tr>
<tr>
<td>Guandalini (JPGN 2013)</td>
<td>279</td>
<td>115</td>
<td>115 (100)</td>
</tr>
<tr>
<td>Gidrewicz (Am J Gastroenterol 2015)</td>
<td>775</td>
<td>263</td>
<td>256 (97)</td>
</tr>
</tbody>
</table>
Main aims for PED gi in CD are:

• Management of Potential CD children
  • Prevention of CD
Potential coeliac disease

Presence of CD-specific antibodies and compatible HLA, but without histological abnormalities in duodenal biopsies. May or may not have symptoms and signs. May not develop a gluten-dependent enteropathy later

(Husby et al, 2012)
Questions

1. Which are the **clinical and laboratory features** of potential CD?

2. Are these features different in **Marsh 0 vs Marsh 1** potential CD?

3. Which is the **natural history** of this condition?
Questions

Should it be treated by **GFD**?

Decision should be based on:

- Documented benefit from GFD or demonstration of increased risk of complications on normal diet

- More precise data about long term evolution (percentage of patients evolving to villous atrophy)
Potential Celiac Disease
Progression of the study cohort

331 Enrolled

GFD

48 symptoms

9 parents choice

274 asymptomatic followed on a gluten containing diet

GFD

35 symptoms

42 Villous atrophy

197 Still on a gluten containing diet after 9 years
Potential Celiac Disease
Clinical, histological and serological features (331 patients)

- 14.6% of patients with CD diagnosis 2001-2016
- Age: 6.3 years (range: 1.1-17.84),
- 222 girls (67.1%)
- Clinical: 48 symptomatic (14.5%), 123 (37.1%) at-risk groups (50 autoimmune, 73 first degree relatives)
- Histology: 34.4% Marsh 0, 61.3% Marsh 1
- Diet: normal daily gluten intake
Trend of serological marker during the follow up

Anti-TG2 variations:
- Negative 32.5%
- Fluctuant 33.5%
- Persistently positive 33.9%
Will all become coeliac?

36% of probability to remain potential after 9 years of follow up on a gluten containing diet!!

Most patients (22/42) evolved in celiacs in the first two years of follow up on a GCD.
Biomarkers at time 0 and development of villous atrophy

<table>
<thead>
<tr>
<th></th>
<th>Remained “Potential”</th>
<th>Evolved to Fully Celiac</th>
<th>Sig. (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-TG2 titer</td>
<td>32,38</td>
<td>32,77</td>
<td>0,483</td>
</tr>
<tr>
<td>CD3</td>
<td>35,08</td>
<td>42,62</td>
<td>0,161</td>
</tr>
<tr>
<td>$\gamma\delta$</td>
<td>6,89</td>
<td>10,86</td>
<td>0,000</td>
</tr>
<tr>
<td>CD25</td>
<td>8,59</td>
<td>11,17</td>
<td>0,000</td>
</tr>
<tr>
<td>Presence of anti-TG2 intestinal deposits</td>
<td>58,3%</td>
<td>77,9%</td>
<td>0,004</td>
</tr>
</tbody>
</table>
All have at risk HLA, but still there is a dose-effect p = 0.04
Will all become coeliac?

Major risk to became celiac depend on Marsh grade at time biopsy (p= .009)
Conclusions

“Potential” Coeliac Disease is increasingly diagnosed

Most are (apparently) asymptomatic

With a follow-up up to 9 years, 64% progress to villous atrophy; most in the first 2 years of follow up

Risk factors are
• High genetic risk (HLA)
• Persistence of raised levels of anti-tTG2
• Infiltrative lesion (Marsh 1)
Prevention of CD: what could we do in the 2016?

✓ Genetic risk determination

✓ Preventing strategies
  (time and quantity of gluten during weaning, breastfeeding, less immunoreactive wheat-monocococcus)
Influence of infant nutrition on the risk of developing coeliac disease (CD)

Hogen Esch CE. Eur J Gastroenterol Hepatol. 2010
Randomized Feeding Intervention in Infants at High Risk for Celiac Disease


N Engl j Med 2014; 371; 1304-15
1343 Patients had informed consent provided by a parent

1063 Were positive for HLA-DQ2, HLA-DQ8, or both
280 Were negative for HLA-DQ2 and HLA-DQ8

100 Were excluded
72 Had informed consent withdrawn
25 Entered pilot study
3 Had technical error

963 Underwent randomization

483 Were assigned to gluten group
8 Were excluded
4 Were negative for HLA-DQ2 and HLA-DQ8
2 Were premature
2 Had no first-degree relative with celiac disease

475 Continued in the study
32 Fulfilled the criteria for diagnostic small-bowel biopsies

47 Underwent small-bowel biopsies
4 Did not have clear diagnosis
1 Received diagnosis of celiac disease

480 Were assigned to placebo group
11 Were excluded
9 Were negative for HLA-DQ2 and HLA-DQ8
1 Was premature
1 Had no first-degree relative with celiac disease

469 Continued in the study
53 Fulfilled the criteria for diagnostic small-bowel biopsies

47 Underwent small-bowel biopsies
6 Did not undergo small-bowel biopsies
4 Did not have clear diagnosis
34 Received diagnosis of celiac disease
2 Received diagnosis of celiac disease
80 Received diagnosis of celiac disease
Cumulative incidence: 6% at 3 years
13.5% at 5 years
No statistically significant differences were observed between gluten and placebo group
Females showed an increased risk to develop CD either at 3 years (8.9 vs 3.2%) and at 5 years (15.1 vs 5.9%) compared to males.
More at risk children homozygous for DQ2 (HLA class 1 risk):
14.9% at 3 years and 26.9% at 5 years.
Introduction of Gluten, HLA Status, and the Risk of Celiac Disease in Children

Lionetti E, NEJM 2014;371:1295-303
Conclusions.

• Celiac disease prevalence improves in the last decades all around the world
• New clinical and histological phenotypes are emerging.
• Validate new diagnostic criteria in the future
• Possible preventive strategies could be planned for at risk children.