Celiac disease
Particularities, Problems, Prospects

Ioanna Panayotou
OCTOBER 2014
The celiac “scenario”

Increase of incidence
Delay of diagnosis
Atypical symptoms
<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>INCIDENCE OF DIAGNOSIS</th>
<th>INCIDENCE OF IDENTIFICATION</th>
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<tr>
<td>Brasil</td>
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<tr>
<td>Denmark</td>
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<td>Finland</td>
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<td>Germany</td>
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<td>Italy</td>
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<td>Netherlands</td>
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<td>Sahara</td>
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<tr>
<td>Sweden</td>
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<td>United Kingdom</td>
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<td>USA</td>
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“CD is an immune mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals, characterised by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, HLA-DQ2 and DQ8 haplotypes and enteropathy”
ESPGHAN Guidelines for the Diagnosis of Celiac disease in Children and Adolescents: An Evidence-Based Approach

The ESPGHAN Working Group on Celiac Disease Diagnosis; JPGN. November 2011
AIMS

To evaluate and to study the spectrum of celiac disease
To reply to some specific questions

- Whom to test
- The HLA aspects
- The value of antibodies
- The use of biopsy
- Algorithms
The celiac story

Emphasizes the genetic background of the condition

CD represents a combination of variable characteristics
The Celiac Iceberg

Symptomatic Celiac Disease

Silent Celiac Disease

Latent Celiac Disease

Manifest mucosal lesion

Normal Mucosa

Genetic susceptibility: - DQ2, DQ8
Positive serology
### Types of celiac disease

<table>
<thead>
<tr>
<th></th>
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<th>Potential</th>
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<tr>
<td>Symptoms</td>
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<tr>
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</tr>
<tr>
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Silent CD

“The presence of CD-specific antibodies, HLA and small bowel biopsy findings compatible with CD, but without sufficient symptoms and signs to warrant clinical suspicion of CD.”
## Types of celiac disease

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<tbody>
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<td>Symptoms</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td></td>
</tr>
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<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Serology</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
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</table>

**Latent CD**

“The presence of compatible HLA but without enteropathy in a patient who has had a gluten-dependent enteropathy at some other time of his or her life. The patient may or may not have symptoms and may or may not have CD-specific antibodies”
### Types of celiac disease

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<td>Histology</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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</table>

**Potential CD**

“The presence of CD-specific antibodies and compatible HLA but without histological abnormalities. The patient may or may not have symptoms and signs and may or may not develop a gluten-dependent enteropathy at a late time”
SYMPTOMS

- intestinal
- extraintestinal
## SYMPTOMS

<table>
<thead>
<tr>
<th>Symptom</th>
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<tbody>
<tr>
<td>iron deficiency anaemia</td>
<td>short stature</td>
</tr>
<tr>
<td>anorexia</td>
<td>irritability</td>
</tr>
<tr>
<td>weight loss</td>
<td>liver disease</td>
</tr>
<tr>
<td>abdominal distension</td>
<td>malnutrition</td>
</tr>
<tr>
<td>abdominal pain</td>
<td>constipation</td>
</tr>
<tr>
<td>diarrhea</td>
<td>apthoid ulcers</td>
</tr>
<tr>
<td>delay of puberty</td>
<td>dermatitis herpetiformis</td>
</tr>
<tr>
<td>osteoporosis</td>
<td>arthritis</td>
</tr>
<tr>
<td>neuropathy</td>
<td></td>
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</table>
WHOM TO TEST

GROUP 1. Children and adolescents with symptomatology compatible with celiac disease
GROUP 2. Asymptomatic children and adolescents at high risk to develop celiac disease

- Diabetes mellitus type 1
- Down, Turner, and Williams syndrome
- Autoimmune thyreoiditis
- IgA deficiency
- Autoimmune hepatitis
- 1st degree relatives of patients
CELIAC DISEASE
Diagnostic procedures

- Endoscopy with biopsy
- Endoscopic capsule
- Molecular testing
- MRI enterography
- Enteroscopy
- Confocal microendoscopy
Normal 0  Infiltrative 1  Hyperplastic 2
Partial atrophy 3a  Subtotal atrophy 3b  Total atrophy 3c


1 preinfiltrating stage
2 infiltrating stage (increase of intraepithelial lymphocytes)
3 crypts hyperplasia
4 crypts hyperplasia + villous atrophy (3a, 3b, 3fc)
Biopsy and its role

Histologic changes show patchy distribution or are located exclusively in the bulb

It is important to measure intra-epithelial lymphocytes in Type I

tTG titer is associated with the severity of the tissue damage
The HLA ASPECT

Considering HLA analysis negative results have a great value, (they definitely exclude celiac disease) 30% of healthy population owns haplotypes HLA-DQ2 and/or HLA-DQ8

Identification is more accurate using molecular genetics techniques
Value of ANTIBODIES

anti-tissue trasgloutamonase (IgA -tTG)
anti-endomycial
anti deaminated gliadine peptides

Adequate consumption of gluten
absence of immunosuppression

In IgA DEFICIENCY   IgG tTG ....EMA...DGP

EMA show high specificity
The sensitivity of tTG, increases in parallel with the increase of the titer
DGP show less sensitivity than the others
Results from different labs are not comparable
Endoscopic camera

villi atrophy $\rightarrow$ celiac disease

normal villi $\rightarrow$ endoscopy with biopsy
Σενάριο 1ο: Παιδί/έφηβος με συμπτώματα συμβατά με κοιλιοκάκη

- τTG & ολική IgA
- Θετικά τTG
  - > 10 UNL
  - < 10 UNL
    - EMA (απορρίπτεται) και HLA
      - EMA (+), HLA (+) → CD
      - EMA (+), HLA (-) → False neg HLA? Biopsies?
      - EMA (-), HLA (-) → False pos τTG?

- Νεγατικά τTG
  - Όχι CD
    - IgA deficiency
    - Age < 2yrs
    - Low gluten diet
    - Severe symptoms
    - Related conditions

- Biopsies?
SYMPTOMATIC CHILDREN

**tTG & total IgA**

- **Positive tTG**
  - > 10 UNL → EMA & HLA
    - EMA (+), HLA (+) → CD
    - EMA (+), HLA (-) → False neg HLA? Biopsies?
  - < 10 UNL → EMA & HLA
    - EMA (-), HLA (-) → False pos tTG?
    - EMA (-), HLA (+) → False neg HLA? Biopsies?

- **Negative tTG** → No CD
  - IgA deficiency
  - Age < 2yrs
  - Low gluten diet
  - Severe symptoms
  - Related conditions

**Biopsies**
Symptomatic Children

- tTG & total IgA
  - Positive tTG
    - > 10 UNL
      - EMA & HLA
        - EMA (+), HLA (+) → CD
        - EMA (+), HLA (-) → False neg HLA?
          - Biopsies?
        - EMA (-), HLA (-) → False pos tTG?
        - EMA (-), HLA (+) → Biopsies
          - Marsh 2/3 → CD
    - < 10 UNL
      - EMA & HLA
        - EMA (+), HLA (+) → CD
        - EMA (+), HLA (-) → False neg HLA?
          - Biopsies?
        - EMA (-), HLA (-) → False pos tTG?
        - EMA (-), HLA (+) → Biopsies
          - Marsh 2/3 → CD
  - Negative tTG → No CD
    - IgA deficiency
    - Age < 2yrs
    - Low gluten diet
    - Severe symptoms
    - Related conditions

- EMA & HLA
  - EMA (+), HLA (+) → CD
  - EMA (+), HLA (-) → False neg HLA?
    - Biopsies?
  - EMA (-), HLA (-) → False pos tTG?
  - EMA (-), HLA (+) → Biopsies
    - Marsh 2/3 → CD
SYMPTOMATIC CHILDREN

- tTG & total IgA
  - Positive tTG
    - > 10 UNL
      - EMA & HLA
        - EMA (+), HLA (+): CD
        - EMA (+), HLA (-): False neg HLA? Biopsies?
        - EMA (-), HLA (-): False pos tTG?
        - EMA (-), HLA (+): EMA (+), HLA (-)
  - < 10 UNL
  - Negative tTG
    - IgA deficiency
    - Age < 2yrs
    - Low gluten diet
    - Severe symptoms
    - Related conditions
    - Biopsies
      - Marsh 0/1: False pos serology? False neg biopsy? Further evaluation
      - Marsh 2/3: CD
ASYMPTOMATIC CHILDREN AT RISK
ASYMPTOMATIC CHILDREN AT RISK

HLA

Negative HLA → No CD
ASYMPTOMATIC CHILDREN AT RISK

HLA

Positive HLA

Negative HLA

No CD

tTG & total IgA
ASYMPTOMATIC CHILDREN AT RISK

- HLA
  - Positive HLA
    - tTG & total IgA
  - Negative HLA
    - No CD

- Negative tTG

- False neg serology?
  - IgA deficiency
  - Age < 2yrs
  - Low gluten diet

- IgA deficiency
  - Age < 2yrs
  - Low gluten diet
ASYMPTOMATIC CHILDREN AT RISK

HLA

Positive HLA
Negative HLA

No CD

tTG & total IgA

> 3 UNL
< 3 UNL

Negative tTG

False neg serology?
IgA deficiency
Age < 2yrs
Low gluten diet

IgA deficiency

Age < 2yrs

Low gluten diet
**ASYMPTOMATIC CHILDREN AT RISK**

- **HLA**
  - Positive HLA
  - Negative HLA
    - **No CD**
    - **Negative tTG**
      - < 3 UNL
      - **IgA deficiency**
      - **Age < 2yrs**
      - **Low gluten diet**
    - **> 3 UNL**
      - **Biopsies**
        - Marsh 2/3
          - **CD**
          - False neg serology?
ASYMPTOMATIC CHILDREN AT RISK

HLA

Positive HLA ⇔ Negative HLA → No CD

tTG & total IgA

≥ 3 UNL ⇔ < 3 UNL

Biopsies

Marsh 2/3 ⇔ Marsh 0/1

CD

- False neg serology?
- IgA deficiency
- Age < 2 yrs
- Low gluten diet

Potential CD?
F/U on gluten diet
**ASYMPTOMATIC CHILDREN AT RISK**

- **HLA**
  - Positive HLA
  - tTG & total IgA
    - > 3 UNL
      - Biopsies
        - Marsh 2/3
          - CD
        - Marsh 0/1
          - False pos serology?
          - False neg biopsy?
          - Potential CD?
          - F/U on gluten diet
    - < 3 UNL
      - Negative tTG
        - EMA (+)
          - EMA
          - Marsh 0/1
          - False neg biopsy?
          - Potential CD?
          - F/U on gluten diet
      - Negative HLA
        - NoCD

- **False neg serology?**
- **IgA deficiency**
- **Age < 2yrs**
- **Low gluten diet**
Endoscopic camera... when

Persons with positive antibodies, not willing to undergo biopsy

Evaluate the disease extent and complications
Research PRIORITIES

Determination of the responsible genes
WHOM... WHEN... HOW

New reliable non invasive methods to diagnose and to follow -up patients with celiac disease

www.celiaccenter.org
www.now heat-grtx-now.heat.index.htm
Primary prevention

Breast feeding... tolerance ??
Celiac disease in older children
Higher degree of atypical symptoms
the future

New treatments ...vaccination ...genetically modified wheat .......
What is the natural history of celiac disease (SILENT WITHOUT DIET)
Response of asymptomatic children DQ2-DQ8 to gliadin peptides
Preventing factors
Time of introduction of cereals (immunological response B, th1 to gluten)
Safe amount of gluten in feeds
Quality of life in children with celiac disease
CONCLUSIONS

1. Celiac disease has a wide spectrum of clinical features.
2. Laboratory testing is required in some specific and suggested indications.
3. In symptomatic children, suspicious for celiac disease, tTG is the main investigation.
4. On the other hand asymptomatic children, at risk. HLA testing is necessary.
5. Jejunal biopsy remains the gold standard to diagnose celiac disease in childhood. There are limited circumstances that probably biopsy could be avoided!
CELIAC DISEASE
Thank you