Celiac disease and related food intolerances to cereals

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terminology, synonyma

= celiac disease  (endemic sprue of adults)
= gluten-sensitive enteropathy
= autoimmunity

prevalence: 1/220 prospective,  
1/74  retrospective (1%)  
western world (1-2%)

tropical sprue  infectious or unknown etiology , in underdeveloped or tropical countries, doxycyclin therapy for 6 months
definition of celiac disease

chronic immune-mediated enteropathy of the small intestine, induced by exposition to gluten in foodstuffs in genetically predisposed individuals

(HLA-DQ 2 and/or –DQ 8)
pathophysiological conditions to develop celiac disease

coincidence of at least 3 predisposing factors:

exogenous trigger + mucosal barrier disturbance/defect + genetic predisposition, resulting in an adaptive, but dysregulated pathophysiological immune response

epidemiology of celiac disease in 2012

### gluten

* = glue protein

= collective term for protein mixture

<table>
<thead>
<tr>
<th>Prolamins</th>
<th>50:50</th>
<th>Glutelins</th>
<th>80% of all proteins in grains</th>
</tr>
</thead>
<tbody>
<tr>
<td>soluble in 70% ethanol</td>
<td>soluble in the alkaline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wheat*: gliadin</td>
<td>heat: glutenin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rye: secalin</td>
<td>rye: secalinin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>barley: hordein</td>
<td>barley: hordenin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oats: avenin</td>
<td>oats: avenalin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Amino acids
- Prolin + glutamin

*Wheat allergens, e.g. ω-5 gliadin, water- & salt-insoluble gliadin

Pietzak M. Celiac disease, wheat allergy and gluten sensitivity: When gluten free is not a fad. J Parenteral and Enteral Nutrition 2012; 36(S1): 68S-75S
pathophysiology of celiac disease

**Immunopathological damage of enterocytes induce enteropathy (autoimmunity)**

*Indigestible gliadin peptides* pass intestinal barrier, infiltrate lymphocytes into epithelial layer, and release zonulin. GI peptides are modified by tissue transglutaminase 2, activating T killer cells. Antigen-presenting cells stimulate HLA-DQ2 CD4+ T-helper cells and mature B cells, which produce antibodies against tissue transglutaminase, endomysium, conventional gliadin, deamidated gliadin.

*Note:* Tissue transglutaminase (TTG) is present in many tissues and deamidates proteins and peptides.

Fasano A, Spectrum der Wissenschaft 2010
## different forms of celiac disease

<table>
<thead>
<tr>
<th>celiac disease</th>
<th>symptoms</th>
<th>serology</th>
<th>histology</th>
<th>Marsh</th>
</tr>
</thead>
<tbody>
<tr>
<td>typical</td>
<td>yes – gastrointestinal malabsorption</td>
<td>positive HLA DQ2/8</td>
<td>positive</td>
<td>≥2-3 a-c</td>
</tr>
<tr>
<td>mono- or oligosyptomatic</td>
<td>discrete, (e.g. iron deficiency, growth retardation ...)</td>
<td>positive HLA DQ2/8</td>
<td>positive</td>
<td>1-2</td>
</tr>
<tr>
<td>asymptomatic or silent</td>
<td>no</td>
<td>90% positive HLA DQ2/8</td>
<td>positive</td>
<td>≥1</td>
</tr>
<tr>
<td>atypical</td>
<td>often uncharacteristic symptomatology (extraintestinal)</td>
<td>positive</td>
<td>positive</td>
<td>1-3 a</td>
</tr>
<tr>
<td>latent</td>
<td>asymptomatic or oligosyptomatic during gluten-free diet; previously celiac disease</td>
<td>neg. oder pos. HLA DQ2/8</td>
<td>uncharacteristic to negative</td>
<td>. . . (previously 1-3 a ?)</td>
</tr>
<tr>
<td>potential</td>
<td>no symptoms at presentation (but possible in future)</td>
<td>positive HLA DQ2/8</td>
<td>negative</td>
<td>0</td>
</tr>
<tr>
<td>transient</td>
<td>celiac disease in infancy, remission under diet - later, despite gluten intake no recurrence!</td>
<td>positive HLA DQ2/8</td>
<td>positive</td>
<td>&gt;1</td>
</tr>
<tr>
<td>refractory</td>
<td>yes type 1: normal population IEL type 2: aberrante/premalignant IEL</td>
<td>positive HLA DQ2/8</td>
<td>positive</td>
<td>&gt;1</td>
</tr>
</tbody>
</table>
## Histology
### Marsh-Criteria

<table>
<thead>
<tr>
<th>Marsh</th>
<th>Villi</th>
<th>Crypts (villi : crypts)</th>
<th>Intraepithelial Lymphocytes/100 Epithelial Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marsh 0</td>
<td>normal</td>
<td>normal (v : c &gt;&gt; 3)</td>
<td>0 – 25</td>
</tr>
<tr>
<td>Marsh 1</td>
<td>normal</td>
<td>normal (v : c = &gt;3 : 1)</td>
<td>pathological &gt;40 (suspicious &gt; 25)</td>
</tr>
<tr>
<td>Marsh 2</td>
<td>normal</td>
<td>hyperplastic (v : c = &gt;2 : 1)</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Marsh 3 a</td>
<td>partial atrophy</td>
<td>hyperplastic (v : c = &lt;2 : 1)</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Marsh 3 b</td>
<td>subtotal atrophy</td>
<td>hyperplastic (v : c = &lt;2 : 1)</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Marsh 3 c</td>
<td>complete atrophy</td>
<td>hyperplastic (v : c = &lt;2 : 1)</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Marsh 4</td>
<td>complete atrophy</td>
<td>hypoplastic</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

**Cave:** collagenous celiac disease

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4–5 biopsies from different locations of the duodenum (descending part & 1–2 biopsies from duodenal bulb)

Marsh, Gastroenterology 102, 330, 1992
celiac disease - clinical symptoms

- **typical symptoms**
  - diarrhea
  - weight loss
  - bloating, meteorism
  - obstipation
  - weakness
  - failure to thrive

- **atypical symptoms (often)**
  - iron deficiency, anemia
  - pallor
  - personality changes
  - enamel defects
  - depression, ataxia, epilepsy
  - osteoporosis, arthritis
  - infertility, miscarriage

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### 89 newly diagnosed celiac disease patients

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>iron deficiency</td>
<td>24</td>
</tr>
<tr>
<td>iron deficiency without anemia</td>
<td>22</td>
</tr>
<tr>
<td>often abdominal pain</td>
<td>20</td>
</tr>
<tr>
<td>mood alterations</td>
<td>14</td>
</tr>
<tr>
<td>aphtous stomatitis</td>
<td>9</td>
</tr>
<tr>
<td>loss of appetite</td>
<td>8</td>
</tr>
<tr>
<td>often diarrhoea</td>
<td>7</td>
</tr>
<tr>
<td>growth retardation</td>
<td>6</td>
</tr>
<tr>
<td>meteorismus</td>
<td>4</td>
</tr>
<tr>
<td>obstipation</td>
<td>2</td>
</tr>
<tr>
<td>delayed puberty</td>
<td>2</td>
</tr>
<tr>
<td>decreased serum albumine</td>
<td>2</td>
</tr>
</tbody>
</table>

Catassi et al., Acta Paediatr. 85, S412, 29, 1996

- nowadays **often unspecific symptoms**, - not rarely, adverse food reactions differential diagnoses – food intolerance or gastrointestinal food allergy
diagnostics of celiac disease

obligatory diagnostics
1. serology (antibody diagnostics) & total IgA level
2. endoscopy & histology
3. HLA-detection DQ2/8

adjunctive diagnostics
4. transabdominal ultrasonography
5. H2-, C13-breath test, (xylose test)
5. capsule endoscopy & modern enteroscopy (double - or single balloon enteroscopy, spiral enteroscopy)
6. MRT-Sellink small bowel, CT-Abdomen

## Modern Serological Tests for Celiac Disease

<table>
<thead>
<tr>
<th><strong>1. – 3. Celiac Disease Specific Antibodies</strong></th>
<th><strong>serum IgA Antibody</strong></th>
<th><strong>serum IgG Antibody</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Tissue Transglutaminase 2</strong> (anti-TG2 IgA)</td>
<td>1. <strong>Tissue Transglutaminase 2</strong> (anti-TG2 IgG)</td>
<td></td>
</tr>
<tr>
<td>2. <strong>Anti-Endomysial Antibody</strong> (EMA IgA)</td>
<td>2. <strong>Anti-Endomysial Antibody</strong> (EMA IgG)</td>
<td></td>
</tr>
<tr>
<td>3. <strong>Anti-Gliadin Deamidated</strong> (anti-DGP IgA)</td>
<td>3. <strong>Anti-Gliadin Deamidated</strong> (anti-DGP IgG)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac Disease (typical, oligo- and/or monosymptomatic)</td>
<td>95-100%</td>
<td>90-97%</td>
</tr>
<tr>
<td>Silent Celiac Disease</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Latente Celiac Disease</td>
<td>Borderline - negative</td>
<td>30-60%</td>
</tr>
<tr>
<td>Food Allergy Irritable Bowel Syndrome (IBS)</td>
<td>(borderline) – negative (borderline) – negative</td>
<td>Partially detectable 15-40% Partially detectable 30-36%</td>
</tr>
<tr>
<td>Normal Population</td>
<td>Negative</td>
<td>25-30%</td>
</tr>
</tbody>
</table>
serology in celiac disease

Serology with celiac disease specific antibodies is only useful, if a sufficient gluten ingestion is present within the last 2-3 months = 0,5-1g gluten/kg b.w. ! adults up to 40 g/day (at least 2 slices of white bread) children up to 15g/day

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (Range)</th>
<th>Specificity (Range)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA anti-tTG antibodies</td>
<td>&gt;95.0 (73.9–100)</td>
<td>&gt;95.0 (77.8–100)</td>
<td>Recommended as first-level screening test</td>
</tr>
<tr>
<td>IgG anti-tTG antibodies</td>
<td>Widely variable (12.6–99.3)</td>
<td>Widely variable (86.3–100)</td>
<td>Useful in patients with IgA deficiency</td>
</tr>
<tr>
<td>IgA antiendomysial antibodies</td>
<td>&gt;90.0 (82.6–100)</td>
<td>98.2 (94.7–100)</td>
<td>Useful in patients with an uncertain diagnosis</td>
</tr>
<tr>
<td>IgG DGP</td>
<td>&gt;90.0 (80.1–98.6)</td>
<td>&gt;90.0 (86.0–96.9)</td>
<td>Useful in patients with IgA deficiency and young children</td>
</tr>
<tr>
<td>HLA-DQ2 or HLA-DQ8</td>
<td>91.0 (82.6–97.0)</td>
<td>54.0 (12.0–68.0)</td>
<td>High negative predictive value</td>
</tr>
</tbody>
</table>

* Data are from Husby et al. and Giersiepen et al. DGP denotes deamidated gliadin peptides, and tTG tissue transglutaminase.

Fasano A NEJM 2012
asymptomatic patients with increased risk of celiac disease conditions for celiac disease screening

- first-degree relatives of celiac disease patients
- diabetes mellitus type 1
- selective IgA deficiency
- Dermatitis herpetiformis Duhring (DH)
- vitiligo
- autoimmune thyreoiditis
- autoimmune disease of liver and bile system
- **genetic syndromes:**
  - trisomie 21 (Down syndrome)
  - Ullrich-Turner-syndrom
  - Williams-Beuren-syndrom
celiac disease - complications

- **symptoms due to malabsorption**
  - hypovitaminose (vit A, D, K, E) and vit B1, B12 and others
  - tetany, muscle cramps, osteomalacia, bleeding, polyneuropathy

- **collagenous celiac disease**
  - thick collagen layer under epithelial cells - steroids

- **refractory celiac disease with progredient weight loss**
  - no response to gluten-free diet, poor prognosis

- **risk of malignancy: 1.29 fold increased**
  - gastrointestinal neoplasm 1.85 fold
  - lymphoproliferative disease 4.8-6.42 fold
  - breast or lung cancer 0.35 / 0.34 fold

- **secondary autoimmunity**
  - polyendocrinopathy, thyreoiditis

- **secondary carbohydrate malassimilation**

West J, BMJ 2004
Silano M, Dig Dis Sci 2007
differential diagnoses of celiac disease and intolerance to cereals

- frukto-oligosaccharides, -polysaccharides (fructans)
- incomplete starch digestion
- small intestinal bacterial overgrowth (SIBO)
- carbohydrate malassimilation

- dysbiosis
- bacterial histamine?
- IEL, villus atrophy

- gut associated lymphoid tissue (GALT)
- D A O - ? - HNMT

- carbohydrate malassimilation
- bacterial histamine?
- IEL, villus atrophy

- HLA DQ2, DQ8
- atopy - entopy

- DAO deficiency
- histamine degradation ↓
- mast cell hyperplasia
- histamine production ↑

- malabsorption
- allergy

Kaukinen K et al. Intolerance to cereals is not specific for celiac disease. Scan J Gastroenterol 2000; 35: 942-946
therapy of celiac disease

1. avoidance of the exogenous trigger (therapy of choice)
   • gluten-free diet, lifelong

2. modulation of immune response (second choice)
   only when gluten-free diet fails (refractory celiac disease, type I >> type II)
   • glucocorticoids
   • azathioprin, tacrolimus
   • case reports anti-TNF

3. symptomatic therapy (malabsorption)
   • substitution Ca, Fe, vitamin D, folat, . . .
   • carbohydrate reduced diet (lactose, fructose, sorbit, ...)
   • medium chain fatty acids initially, glutamine, diet respecting other intolerances, e.g. histamine, ...

4. new therapeutic developments in future?
   • gliadin-digestion (enzymes), synthetic polymers, genetically modified grains
   • probiotics (VSL 3), improvement of gut barrier, blockage of HLA DQ2/8
   • tannins, adstringents coupled with antibodies (IgY) against peptic-tryptic digested gliadin (glutosin)
therapy of celiac disease

how much gluten is gluten-free?

Codex Alimentarius (1st January 2012):

„very low gluten content“ \(\leq 100 \text{ mg gluten/kg} \)

„gluten-free“ \(\leq 20 \text{ mg/kg} \)

„food products with oats“ \(\leq 20 \text{ mg/kg Gluten} \).

at diagnosis and 4 weeks later

nutrition counseling and education of patient and family

structured dietary advice, food lists of celiac disease society,

alternative products should be offered (millet, maize, rice, ...)

controversy oats?

- only under medical observation (gastroscopy after 3-6 months and in stable disease)

gluten challenge (special situations)

oral gluten application, 0,5-1g gluten/kg b.w.

adults up to 40 g/d - children up to 15g/d for 2-4-8 weeks

http://dzg-online.de

eating from internet

www.glutenfreigeniessen.de

www.querfood.de

www.glfparadies.de
therapy of celiac disease – new treatment options

- Reduce gluten exposure
  - Genetically modified grains
  - Enzyme degradation*
  - Synthetic polymers
- Decrease intestinal permeability
  - Zonulin inhibition (larazotide)**
- Decrease immune activation
  - TTG* inhibition (reduce gliadin deamidation)
  - HLA# DQ2/DQ8 blockade
  - Cytokine modulation/blockade

bacterial endopeptidases for gluten digestion
TTG = Tissue-transglutaminase 2

De Angelis M et al. VSL#3 probiotic preparation has the capacity to hydrolyze gliadin polypeptides responsible for celiac sprue. Biochim Biophys Acta 2006, 1762:80-93

Tennyson CA et al Therapeutic Advances in Gastroenterology 2009
algorithm for celiac disease diagnosis

Guijral N et al
World J Gastro-enterol 2012