Celiac Disease and Enteropathy-Associated T-Cell Lymphoma
Celiac Disease

Celiac disease is a systemic immune-mediated disorder triggered by dietary gluten in genetically susceptible persons.
The Celiac Iceberg

Prevalence: 0.3% in Germany, 2.4% in Finland
Pathogenesis of Celiac Disease

Harris LA, et al., Gastrointest Endoscopy 2012, 76:625
## Clinical Presentation

### Four clinical types of celiac disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
<th>Sero-logy</th>
<th>HLA Type</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>Diarrhea, weight loss...</td>
<td>+</td>
<td>+</td>
<td>Atrophy</td>
</tr>
<tr>
<td>Atypical</td>
<td>Anemia, osteoporosis, arthritis, infertility, fatigue, abnormal transaminases</td>
<td>+</td>
<td>+</td>
<td>Variable</td>
</tr>
<tr>
<td>Silent</td>
<td>Asymptomatic, recognized based on screening</td>
<td>+</td>
<td>+</td>
<td>Atrophy</td>
</tr>
<tr>
<td>Potential</td>
<td>Variable (none or minor)</td>
<td>+</td>
<td>+</td>
<td>No Atrophy</td>
</tr>
</tbody>
</table>
Celiac Disease

Gastrointestinal Symptoms

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Children & adults

- Chronic diarrhea
- Weight loss
- Abdominal distension
- Vitamin deficiency
- Abdominal pain

40% of patients only!
# Celiac Disease

**GI signs and conditions associated with CD**

<table>
<thead>
<tr>
<th>Area of GI tract</th>
<th>Sign or condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Defects in dental enamel, atrophic glossitis, recurrent aphthous ulcers</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Refractory GERD, eosinophilic esophagitis</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Recurrent pancreatitis</td>
</tr>
<tr>
<td>Liver</td>
<td>Transaminitis, autoimmune hepatitis, steatohepatits, PBC, PSC</td>
</tr>
<tr>
<td>Intestine</td>
<td>IBD (Ulcerative colitis&gt;Crohns)</td>
</tr>
</tbody>
</table>
Celiac Disease

*Non-GI diseases associated with CD*

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>Dermatitis herpetiformis</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>Thyroiditis, Sjögren's S., type 1 diabetes, rheumatoid arthritis</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>Infertility (IVF!), recurrent abortions, endometriosis</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Depression, migraine, peripheral neuropathy</td>
</tr>
<tr>
<td>Immunologic</td>
<td>IgA deficiency</td>
</tr>
<tr>
<td>Bone</td>
<td>Vit. D/calcium deficiency, osteoporosis</td>
</tr>
</tbody>
</table>
Celiac Disease

Diagnosis

*The golden standard is:*

- Endoskopy with multiple duodenal biopsies
- Serology : IgA tissue transglutaminase
Diagnosis of Celiac Disease

Clinical suspicion

IgA tissue transglut./ Serum IgA

Duodenal biopsy*

   Celiac disease confirmed

   Other enteritis? HLA?*

3. Histo neg + Sero pos.
   Rebiopsy

   No celiac disease

*HLA-DQ2: 90%; HLA-DQ8: 5-7% <5% weder noch!

Diagnosis of Celiac Disease

Histology positive – Serology negative

1. Serology may be negative in up to 5%
2. 2-3% of patients have IgA deficiency
3. Histology false positive

Message: Histology may overrule serology!

Histologie negativ – Serologie positiv

1. Rebiopsy, including duodenal bulb!!
2. Serology often false positive using IgG allergy test
Who has increased risk and should be tested?

- Malabsorption, chronic diarrhea
- Anemia (iron def.)
- Vitamin D deficiency
- Osteoporosis
- Dyspepsia
- Irritable bowel syndrome
- Lymphocytic colitis, 15-27%
- Diabetes mellitus type 1, 3-16%
- Autoimmunthyroiditis, 5%, -hepatitis
- Dermatitis herpetiformis
- 1. degree relative, 10-15%
- Unexplained infertility, chronic fatigue syndrome, 2%

Clin Exp Gastroenterol 2011; 4:297
**Histological Diagnosis of Celiac Disease**

- 4-6 biopsies, including duodenal bulb
- Villous atrophy (mild, moderate, severe)
- Crypt hyperplasia
- Increase of intraepithelial lymphocytes (IEL)
  > 40 IEL /100 enterocytes (included in report!)*

  - Plasmacytosis in lamina propria
  - Alteration of surface epithelium & increase in crypt mitosis
  - Reduction of goblet cells, epith. flattening, incr. vulnerab.

*Immunohistochemistry (CD3) not required*
More important than a fixed cutoff number may be an understanding between the pathologist and the clinician as to what is significant. Communication supersedes the value of an exact count or threshold.

But

Increase of IELs is the most sensitive and therefore the single most important histologic feature of celiac disease.

Harris LA, et al., Gastrointest Endoscopy 2012, 76:625
Duodenal Endoscopy of Atrophic Mucosa

Cobblestone or mosaic

Scalloping of mucosal folds
Normal Histology & Perfect Orientation

IEL < 40/100 Enterozyten
# Modified Marsh Classification 1999

<table>
<thead>
<tr>
<th></th>
<th>type 1</th>
<th>type 2</th>
<th>type 3a</th>
<th>type 3b</th>
<th>type 3c</th>
</tr>
</thead>
<tbody>
<tr>
<td>IEL</td>
<td>&gt;40</td>
<td>&gt;40</td>
<td>&gt;40</td>
<td>&gt;40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Crypts</td>
<td>⊥</td>
<td>hyperpl</td>
<td>hyperpl</td>
<td>hyperpl</td>
<td>hyperpl</td>
</tr>
<tr>
<td>Villi</td>
<td>⊥</td>
<td>⊥</td>
<td>mild atrophy</td>
<td>severe atrophy</td>
<td>absent</td>
</tr>
</tbody>
</table>

*Oberhuber et al, Eur J Gastroenterol Hepatol 1999, 11:1185*
**Type 1**

Celiac disease patient with minimal gluten ingestion

First degree relative of CD patient, derm.herpet. Duhring
Celiac disease-Histology (Oberhuber et al.)

Typ 2

Typ 3a/b

Typ 3c

Typ 3c
Celiac disease Histology Type 3c

Flat mucosa, damaged epithelial surface, plasmacytosis of lamina propria
Quantification of IEL is most important diagnostic step in histological CD-diagnosis

40-50 IEL/100 Enterozyten

Where else IEL ↑?
- Giardiasis
- Postinfectious (viral!)
- H. Pylori gastritis
- Protein allergies
- Autoimmune diseases
- NSAID
- Autoimmune enteropathy
52 External „Celiac Disease“ Cases for Review

<table>
<thead>
<tr>
<th>Final diagnoses</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac Disease</td>
<td>18</td>
<td>34.6</td>
</tr>
<tr>
<td>Irritable bowel syndrome (IBS)</td>
<td>11</td>
<td>21.2</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>5</td>
<td>9.6</td>
</tr>
<tr>
<td>Potential CD</td>
<td>4</td>
<td>7.7</td>
</tr>
<tr>
<td>No CD</td>
<td>4</td>
<td>7.7</td>
</tr>
<tr>
<td>IBS + fructose intolerance</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Post infection</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Iron deficient anemia</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Fructose/lactose intolerance</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>NSAID</td>
<td>1</td>
<td>1.9</td>
</tr>
</tbody>
</table>
**Recommendation of Elements Contained in the Celiac Disease Pathology Report**

- Quality and orientation of biopsies
- Number and location of biopsies taken
- Duodenal bulb included?
- Shape of villi and crypts
- Number of IEL/100 enterocytes
- Type according to modified Marsh classification
(Long-term) Complications of (untreated) celiac disease

- Neoplastic diseases (1.3:1)
- **Refractory celiac disease (2%)**
- **Lymphoma (EATCL)**
- Small bowel cancer
- Oropharyngeal Cancer
- Unexplained infertility (12%)
- Osteoporosis
Interleukin 15: A Key to Disrupted Intraepithelial Lymphocyte Homeostasis and Lymphomagenesis in Celiac Disease

JEAN-JACQUES MENTION,* MÉLIKA BEN AHMED,* BERNADETTE BÈGUE,* ULLAH BARBE,* VIRGINIE VERKARRE,*,† VAHID ASNAFI,§ JEAN-FRÉDÉRIC COLOMBEL,‖ PAUL-HENRI CUGNENC,‖ FRANK M. RUEMMELE,* ELISABETH MCINTYRE,§ NICOLE BROSSE,** † CHISTOPHE CELLIER,*,** and NADINE CERF-BENSUSSAN*  
*INSERM EMI-0212, Faculté Necker, Paris; †Pathology and §Hematology, Hôpital Necker-Enfants Malades, Paris; †Department of Gastroenterology, Hôpital Huriez, Lille; and †Surgery and †Gastroenterology, Hôpital Georges Pompidou, Paris, France

Gastroenterology 2003, 125:730
Expansion of IELs

IL-15
IL-15 induces:

- Expansion of IELs
- IEL-expression of CD94
- Activation of IELs
- Cytolytic IELs destroy epithel cells and cause villous atrophy
- Anti-apoptotic pathway in IELs*
- Inhibition of TGF-β signalling

*Malamut G, et al., 2010, J Clin Invest 120:2131
Intraepithelial Lymphocytes (IEL)

$\alpha\beta$ TCR+, CD3+, CD2+, CD7+, CD5±, CD8+, CD56-, CD4-

Intraepithelial lymphocytosis is characteristic of:

- Celiac disease
- Refractory celiac disease
- CD-associated EATCL
**Refractory Celiac Disease**

Malabsorption syndrome of adults around 50y, with CD histology in spite of strict adherence to GFD for 6-12 months,

Complications: ulcerative jejunitis, EATCL
# Two Types of Refractory Celiac Disease

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunophenotype</td>
<td>normal</td>
<td>aberrant, CD8-</td>
</tr>
<tr>
<td>TCR-clonality</td>
<td>poly/oligo</td>
<td>monoclonal</td>
</tr>
<tr>
<td>Risk of EATCL</td>
<td>low</td>
<td>50%</td>
</tr>
</tbody>
</table>
Immunolog. Phänotyp der IEL bei Zöliakie

Normal

Aberrant

CD3+

CD3+

CD8+

CD8-
TCR Clonality in refractory CD

Typ I

Poly (oligo-) klonal

Typ II

Monoklonal
COELIAC DISEASE

Refractory coeliac sprue is a diffuse gastrointestinal disease

V Verkarre, V Asnafi, T Lecomte, N Patey Mariaud-de Serre, M Leborgne, E Grosdidier, C Le Bihan, E Macintyre, C Cellier, N Cerf-Bensussan, N Brousse

Gut 2003;52:205-211

Lymphozytäre Gastritis
**Refractory CD**

- Histology as in uncomplicated CD
- Immunophenotype depends on RCD type
- IEL clonality depends on RCD type
- Disseminated along the entire GI tract*
  - Lymphocytic gastritis
  - Lymphocytic colitis

*Verkarre et al., Gut 52:205, 2003*
Conclusions

- Pathologist plays a leading role in CD diagnosis
- Collaboration with gastroenterologist essential
- Diagnosis of CD changes life style of patient
- Villous tip counting method preferable
- Type 1 lesion may not represent celiac disease
- Standardization of pathology report recommended
- Refractory CD requires IHC & clonality studies
Diagnostik des intestinalen T-Zell-Lymphoms vom Enteropathie Typ

1. Makroskopie

2. Histologie

3. Immunhistochemie

4. Molekularbiologie
Classification according to Corazza 2005

<table>
<thead>
<tr>
<th>Corazza</th>
<th>Morphology</th>
<th>Oberhuber</th>
<th>IEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>Normal architecture</td>
<td>Type 1 und 2</td>
<td>&gt;25</td>
</tr>
<tr>
<td>Grade B1</td>
<td>Atrophy, Ratio &lt; 3:1</td>
<td>Type 3a und 3b</td>
<td>&gt;25</td>
</tr>
<tr>
<td>Grade B2</td>
<td>Total atrophy</td>
<td>Type 3c</td>
<td>&gt;25</td>
</tr>
</tbody>
</table>
### Table 5: Definite Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>%</th>
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<tr>
<td>Lactose malabsorption</td>
<td>5</td>
<td>9.6</td>
</tr>
<tr>
<td>Celiac disease ruled out</td>
<td>4</td>
<td>7.7</td>
</tr>
<tr>
<td>Potential celiac disease</td>
<td>4</td>
<td>7.7</td>
</tr>
<tr>
<td>IBS + fructose malabsorption</td>
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</tr>
<tr>
<td>Post infection</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Functional dyspepsia</td>
<td>2</td>
<td>3.8</td>
</tr>
<tr>
<td>Combined fructose-lactose malabsorption</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>NSAID-induced colitis</td>
<td>1</td>
<td>1.9</td>
</tr>
</tbody>
</table>