Celiac Disease

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Contents

• Cases
• Definition
• Etiopathogenesis
• Pathology
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• Management of the disease
• Management of complications
Case I

• Five year old boy was brought to your clinic for decreased appetite and headache.
• You find drop in Hb with a low MCV and low iron parameters.
• The child is a normal delivery, with normal dietary habits, normal blood lead level and stool is negative for occult blood.
• Next?
Case II

• 27 year old woman came to your clinic for gas and bloating after eating milk and ice-cream.
• She has heavy menstrual bleeding, has mild anemia with low iron parameters.
• Next?
Case III

• You are the fourth doctor to see a 54 year old woman for diarrhea and abdominal pain.
• She was diagnosed with IBS, underwent twice EGD+colonoscopies with no biopsies.
• She did not benefit from antispasmodics, antidiarrheals.
• What is next?
Case IV

• 65 year old man with 15 year history of celiac disease visits your clinic, as he has diarrhea despite the gluten-free diet for the last 8 months.

• Diarrhea is associated with 15 lbs weight loss.
Definition

• Malabsorption syndrome secondary to gluten sensitivity.

• Gluten is found in wheat, rye and barley.

• Certain medicines and vitamins also contain gluten.

• Immune response against gluten results in intestinal damage.
Etiopathogenesis

- Gluten: Storage form of wheat proteins
- Alcohol soluble fraction: Gliadin
- Gliadin is not completely digested.
- T lymphocyte responses against gliadin, expressed by intestinal epithelial cells in the right HLA context.
- Tissue transglutaminase modifies the gliadin.
Celiac Disease Requires Genetic Predisposition and Environmental Factors

Etiopathogenesis II

Native gliadin peptide \( \xrightarrow{tTG} \) Deamidated gliadin peptide \( \xrightarrow{\Delta(-)} \)

\( \xrightarrow{DQ2/DQ8} \) T-cell receptor

\( \xrightarrow{CD4} \) Interferon \( \gamma \) \( \xrightarrow{\text{Destructive intestinal lesion}} \)

Antigen presenting cell

Etiopathogenesis III

Jabri B et al. Lancet 2003
Pathology

Upper GI Tract
- Iron
- Calcium
- Thiamine
- Folate
- Lactose

Lower GI Tract
- Vitamin B12

Upper GI Tract
- Celiac disease

Lower GI Tract
- Crohn’s disease

http://digestive.niddk.nih.gov/ddiseases/pubs/celiac
Epidemiology

- Disorder of young to middle aged females
- It may present in old age
- Overlap btw. clinical symptoms and serology.
- Frequent disorder of Northern or Western European descends.
# High Frequency of Positive Serology for Celiac Disease in the U.S.

- First Degree Relatives: 4.55%
- Second Degree Relatives: 2.59%
- Symptomatic Adults At Risk: 1.47%
- Symptomatic Children At Risk: 4.00%
- Not At Risk Subjects: 0.75%

Clinical Presentation

- Gas/bloating
- Malodorous diarrhea
- Bone and joint pain
- Tingling in hands or feet
- Muscle cramps
- Irritability
- Weakness, fatigue
- Weight loss
- Infertility
Clinical Presentation II

- Type I Diabetes Mellitus
- Endocrinopathies
- Down syndrome
Strong Association btw. Celiac Disease and Type I DM

Table 1. Association Results for Celiac Risk Variants Genotyped in Type 1 Diabetes Case-Control and Family Collections.

<table>
<thead>
<tr>
<th>Candidate Gene and SNP</th>
<th>Chromosome</th>
<th>Genomewide Association Study of Loci in Celiac Disease</th>
<th>Minor Allele</th>
<th>Allele Frequency Control Subjects</th>
<th>Type 1 Diabetes Results</th>
<th>Combined P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Odds ratio (95% CI) P value</td>
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<tr>
<td></td>
<td></td>
<td>Case subjects control subjects</td>
<td></td>
<td></td>
<td>Case subjects control subjects</td>
<td></td>
</tr>
<tr>
<td>RGS1</td>
<td>1q31</td>
<td>0.72 (0.65–0.79) 2.58×10⁻¹¹</td>
<td>C</td>
<td>0.166 0.182</td>
<td>0.89 (0.84–0.95) 1.23×10⁻⁴</td>
<td>0.91 (0.82–1.00) 0.04</td>
</tr>
<tr>
<td>IL1RAP</td>
<td>2q12</td>
<td>1.29 (1.19–1.40) 8.49×10⁻¹⁰</td>
<td>A</td>
<td>0.220 0.221</td>
<td>0.98 (0.93–1.03) 0.42; 2 df, 0.01</td>
<td>0.87 (0.78–0.96) 0.008; 2 df, 0.006</td>
</tr>
<tr>
<td>CCR3</td>
<td>3p21</td>
<td>1.21 (1.13–1.30) 3.41×10⁻⁷</td>
<td>A</td>
<td>0.321 0.301</td>
<td>1.09 (1.04–1.14) 3.40×10⁻⁴</td>
<td>1.04 (0.95–1.13) 0.39</td>
</tr>
<tr>
<td>IL12A</td>
<td>3q25</td>
<td>1.35 (1.23–1.49) 1.07×10⁻⁸</td>
<td>G</td>
<td>0.123 0.123</td>
<td>1.00 (0.93–1.07) 0.96</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.21 (1.15–1.32) 5.24×10⁻⁸</td>
<td>G</td>
<td>0.451 0.443</td>
<td>1.04 (0.99–1.08) 0.15</td>
<td>ND</td>
</tr>
<tr>
<td>LPP</td>
<td>3q28</td>
<td>1.23 (1.15–1.31) 5.33×10⁻⁹</td>
<td>T</td>
<td>0.451 0.456</td>
<td>1.00 (0.95–1.04) 0.82</td>
<td>ND</td>
</tr>
<tr>
<td>IL2-IL21</td>
<td>4q27</td>
<td>0.71 (0.63–0.80) 2.82×10⁻¹³</td>
<td>T</td>
<td>0.165 0.176</td>
<td>0.95 (0.89–1.00) 0.06</td>
<td>ND</td>
</tr>
<tr>
<td>TAGAP</td>
<td>6q25</td>
<td>1.21 (1.13–1.30) 6.71×10⁻⁸</td>
<td>T</td>
<td>0.414 0.437</td>
<td>0.92 (0.88–0.96) 7.90×10⁻⁵</td>
<td>0.86 (0.80–0.92) 2.71×10⁻⁵</td>
</tr>
<tr>
<td>SH2B3</td>
<td>12q24</td>
<td>1.21 (1.12–1.29) 1.33×10⁻⁷</td>
<td>A</td>
<td>0.544 0.484</td>
<td>1.28 (1.22–1.35) 2.72×10⁻⁴</td>
<td>1.25 (1.15–1.36) 5.08×10⁻⁸</td>
</tr>
</tbody>
</table>

* Celiac disease loci that met the criteria for genomewide significance (P<5.00×10⁻⁷) were tested in type 1 diabetes collections. SNP denotes single-nucleotide polymorphism, and ND not done.
† Data are from Hunt et al.¹⁰
‡ P values were calculated with the use of the Wald test.
§ The 2-df test is reported for P values when there was a significant difference between the model for genotypic effects and that for multiplicative allelic effects so that the multiplicative model was not the appropriate one.
¶ These loci have previously been examined for their possible sharing between celiac disease and type 1 diabetes, with strong support for an association in SH2B3 on chromosome 12q24 (same SNP, same allele direction),¹⁰ since this locus is an established risk determinant for type 1 diabetes.¹

Strong Association btw. Celiac Disease and Type I DM

- Convincing Evidence of Shared Association
- Suggestive Evidence of Shared Association
- Type I DM Only
- Celiac Disease Only

A Diabetic Patient Presents With Gas, Bloating and Diarrhea:

- Infectious Diarrhea
- Gastroparesis
- Slow Intestinal Motility
- Small Intestinal Bacterial Overgrowth
- Celiac Disease
Differential Diagnosis

- Abetalipoproteinemia
- Radiation enteritis
- Amyloidosis
- Bacterial overgrowth
- Common variable immune deficiency
- Crohn’s disease
- Eosinophilic enteritis
- Lymphangiectasia
- Lymphoma
- Tropical sprue
- Whipple’s disease
Diagnosis

• Clinical presentation
• Serology
• Endoscopic findings
• Histopathology
Clinical Diagnosis of Celiac Disease

• Typical Symptoms

• Gluten-free Diet

• Improvement of Symptoms
Serology in Celiac Disease

- Anti-gliadin (IgG, IgA)
- Anti-endomyseal (IgG, IgA) (EMA)
- Anti-tissue transglutaminase (IgG, IgA) (tTG)
- Total IgA
IgA Class Anti-Gliadin Antibodies Are More Frequent in Individuals With IBS

EMA And TTG Antibodies Are More Frequent in Individuals With IBS

Positive Biopsies for Celiac Disease in IBS Patients

Endoscopy in Celiac Disease

- EGD with random biopsies (usually 6)

Normal Duodenum

Scalloping

Scalloping

Ulceration

Management

• Gluten-free Diet
• Dietary Modifications:
  – Lactose-free diet
  – Supplementation with iron, folic acid
  – Treatment or prevention of osteoporosis

• Immune Suppression:
  – Corticosteroids
  – Azathioprine or 6-mercaptopurine
Management II

- No more wheat, barley, oat or rye.
- Rice, soy, sorghum, millet, potato, corn allowed.
- Learning:
  - http://www.celiac.org/
  - http://digestive.niddk.nih.gov/ddiseases/pubs/celiac/#examples
Complications

• Bone Disease
• Malignancy
• Neuropsychiatric Disorders
• Fertility and Reproduction
• Dermatitis Herpetiformis
Skeletal Problems in Celiac Disease

- Osteopenia
- Fractures
- Screening for osteopenia: Not everyone
- Treatment: Calcium, vitamin D and biphosphonates
- Gluten-free diet
Malignancy in Celiac Disease

- Small intestinal adenocarcinoma
- T cell lymphoma

- Clonal expansion of T cells.

- Gluten-free diet “may” reduce the risk of malignancy.
Dermatitis Herpetiformis

- Vesicular skin lesions on extensor surfaces.
- Responds to gluten-free diet and Dapson.

Neuropsychiatric Problems

• Neurological Problems:
  – Peripheral neuropathy
  – Autonomic neuropathy

• Psychiatric Problems:
  – Anxiety and Depression

• Responds to gluten-free diet.
Case II

• 27 year old woman came to your clinic for gas and bloating after eating milk and ice-cream.
• She has heavy menstrual bleeding, has mild anemia with low iron parameters.
• Next?
Case IV

• 65 year old man with 15 year history of celiac disease visits your clinic, as he has diarrhea despite the gluten-free diet for the last 8 months.

• Diarrhea is associated with 15 lbs weight loss.