Chapter 8

Autoimmune Polyendocrine Syndromes
“Th17” Anti-Cytokine Autoantibodies (IL-17A, IL17F, IL-22) and abnormal Th17 T cell function Associated with Mucocutaneous Candidiasis of APS-1

Kisand...Meager et al Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. J Exp Med 2010 207:299-308


Ahlgren...Lobell et al Increased IL-17A secretion in response to Candida albicans in autoimmune polyendocrine syndrome type 1 and its animal model. Eur J Immunol 2011, 41:235-245

**Multiplex Addison’s Families Greater DR3/4-B8**

80%

<table>
<thead>
<tr>
<th>Multiplex</th>
<th>Simplex</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>29</td>
<td>55</td>
<td>3,063</td>
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</table>

**A1 Allele Frequency in DR3/4 B8+ Individuals**

- Addison’s: 17/36
- Diabetes: 400/549
- Controls: 141/174

Less Complete DR3-B8-A1 Extended Haplotype
General Paradigm

- Identify Genetic Susceptibility
- Detect Initial Autoantibodies
- Monitor Metabolic Decompensation
- Treat Overt Disease Prior to Morbidity/Mortality
- Basic/Clinical Research to Allow Prevention
<table>
<thead>
<tr>
<th>Autoimmune Illnesses</th>
<th>Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Celiac Disease:</td>
<td>Diarrhea, weight loss, growth failure, abdominal pain, osteoporosis, anemia</td>
</tr>
<tr>
<td>Hyperthyroid:</td>
<td>Weight loss, feeling warm, anxiety, bulging eyes</td>
</tr>
<tr>
<td>Hypothyroid:</td>
<td>Weight gain, feeling cold</td>
</tr>
<tr>
<td>Pernicious Anemia:</td>
<td>Anemia, movement problems</td>
</tr>
<tr>
<td>Addison’s Disease:</td>
<td>Darkening of skin, loss of weight, dizziness, nausea</td>
</tr>
<tr>
<td>Ovarian Failure:</td>
<td>Premature menopause, hot flashes, infertility</td>
</tr>
<tr>
<td>Myasthenia Gravis:</td>
<td>Muscle weakness, double vision</td>
</tr>
<tr>
<td>Diabetes Mellitus:</td>
<td>Increased urination, thirst, appetite, weight loss, coma</td>
</tr>
</tbody>
</table>
Premature Mortality in Patients with Addison’s Disease: A Population-Based Study
J clin endocrinol Metab 91:4859, 2006

Percent Dying 6.7 yr follow-up; mean start age 52.8

N=507 deaths of 1675 patients
N=199 deaths
Autoimmune Polyendocrine Syndromes

- APS-II (Autoimm Polyendocrine)
- APS-I (AIRE mutation)
- XPID: (Scurfy Mutation)
- Anti-insulin Receptor Abs + “Lupus”
- Hirata (Anti-insulin Autoantibodies)
- POEMS (Plasmacytoma,..)
- Thymic Tumors + Autoimmunity
- Congenital Rubella + DM +Thyroid
Polyendocrine non-Autoimmune Syndromes

- **Wolfram’s Syndrome** – DIDMOAD
  Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness (WFS1 gene mutation on Chromosome 4)

- **Kearns-Sayre Syndrome**
  External Ophthalmoplegia, Retinal Degeneration, Heart Block- Diabetes, Hypoparathyroidism, Thyroiditis reported (Mitochondrial deletions, rearrangements)
APS-Syndromes
Betterle et al. Endocrine Reviews 2002
Neufeld and Blizzard: 1980, Pinchera, in Symposium Autoimmune Endocrine Aspects of Endocrine Disorders

- **APS-I:** $\geq 2$ of Candidiasis, Hypopara, Addison’s
- **APS-II:** Addison’s + Autoimmune Thyroid and/or Type 1 Diabetes (Addison’s must be present)
- **APS-III:** Thyroid Autoimmune + other autoimmune [not Ad, hypopara, candidiasis]
- **APS-IV:** Two or more organ-specific autoimmune, not I, II, or III.
<table>
<thead>
<tr>
<th>APS-I</th>
<th>APS-II</th>
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<tbody>
<tr>
<td>Onset Infancy</td>
<td>Older Onset</td>
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<tr>
<td>Siblings</td>
<td>Multiple Generations</td>
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<tr>
<td>AIRE gene mutated</td>
<td>DR3/4 Associated</td>
</tr>
<tr>
<td>Not HLA Associated</td>
<td>No Defined Immunodeficiency</td>
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<tr>
<td>Immunodeficiency</td>
<td>20% Type 1 DM</td>
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<tr>
<td>Asplenism</td>
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<tr>
<td>Mucocutaneous Candidiasis</td>
<td></td>
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<tr>
<td>18% Type 1 DM</td>
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APS-I

- Autoimmune Polyendocrine Syndrome Type 1
- Autosomal Recessive mutations AIRE (Autoimmune Regulator) gene
- Mucocutaneous Candidiasis/Addison’s Disease/Hypoparathyroidism
- 18% Type 1 Diabetes
- “Transcription Factor” in Thymus
Diagnosis

• Classic criterion
  – At least two:
    • Chronic recurrent mucocutaneous candidiasis
    • Hypoparathyroidism
    • Addison’s disease
    • Prevalence of these criterion by 30 years is only 94%
  – High index of suspicion with individuals presenting with multiple autoimmune disease
  – In siblings one autoimmune disease is required for diagnosis

• Mutation analysis
  – Three most common mutations may miss 5%
AIRE (Autoimmune Regulator) and Percentage Mutations
APS-I: Halonen JCEM 87:2568, 2002

Homogeneously Staining Domain

SAND Domain

Plextrin Homology 1

Plextrin Homology 2

LXLL

LXLL

R257X 967-979del
Y85C L417fsX422
546C+59aa M386fsX422
A21V P398fsX478
R203X C311Y L397fsX478

C322fsX372
<table>
<thead>
<tr>
<th>Exon/Intro</th>
<th>Mutation</th>
<th>Change in coding sequence</th>
<th>No of Alleles</th>
<th>Population</th>
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<tr>
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<td>L28P</td>
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<td>GT&gt;AT, X476</td>
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<td>Exon 13</td>
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<td>Exon 14</td>
<td>1638A&gt;T</td>
<td>X564C+59aa</td>
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</table>
MODEL AIRE Role in Preventing Autoimmunity

Autoreactive thymocyte

TCR

MHC + Peptide

Tolerization of autoreactive thymocyte

Thymic Medullary Epithelial Cells

Self-peptides from "peripheral" antigens

AIRE

Mathis/Benoist
Highly variable expression of tissue-restricted self-antigens in human thymus: Implications for self-tolerance and autoimmunity

Richard Taubert, Jochen Schwendemann and Bruno Kyewski
Division of Developmental Immunology, Tumor Immunology Program, German Cancer Research Center, Heidelberg, Germany
Insulin Message but not GAD67 thymic medullary epithelial expression is tremendously variable and correlates with AIRE message.

Taubert et al, 2007 EJI
Gene Dosage-limiting Role of Aire in Thymic Expression, Clonal Deletion, and Organ-Specific Autoimmunity

Rip-HEL Antigen+CD4 T Cell Receptor anti-HEL Model

X10^7 CD4+Cd8-1G12-CD69-
Halonen JCEM 87:2568,2002
104 APS-I International Series Patients
Greater % Addison’s and Candidiasis with R257X Nonsense (X) Mutation
### APS-I Patients Protected from Diabetes by DQB1*0602

<table>
<thead>
<tr>
<th></th>
<th>Diabetes</th>
<th>Not Diabetic</th>
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<tr>
<td><strong>DQB1*0602+</strong></td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td><strong>DQB1*0602-</strong></td>
<td>13</td>
<td>66</td>
</tr>
</tbody>
</table>

16.4%  

P = .03  

Halonen et al JCEM 87:2574, 2002
NALP5: Hypoparathyroidism
NACHT leucine-rich-protein 5

- >>Expression Parathyroid and Ovary
- 41% Hypopara+APS-1 Positive 0% Not
- APS-1 Animal Model “Have Abs”
- 68% Hypogonad+; 29% not Hypogonad
- Day 3 Thymectomy model +

Kampe et al NEJM 358:1018, 2008
A. 6 Month Evaluation APS-I (Perheentupa)

- Check oral Candida, Autoantibodies, Ca, Pi, Na, K, Mg, Alkaline phosphatase, ACTH, TSH, HCG, renin, HbA1c, Howell-Jolly smear, platelets
- Autoantibodies: 21-hydroxylase (Addison’s), GAD65 (Diabetes), 17-OH, CYP450scc (hypogonadism/Addison’s); Tryptophane hydroxylase (intestine chromaffin cell loss), H/K ATPase and Intrinsic factor (Pernicious anemia), Thyroid peroxidase (hypothyroidism)
- If hypoparathyroid: every 6 to 8 weeks check Ca
- Intense control oral candida (e.g. amphotericin lozenge, fluconazole or ketoconazole if needed) with prompt biopsy suspicious lesion. Careful mouth hygiene with elimination of sharp points of teeth and plastic materials from mouth.
- No live virus immunization
- Patient web site: http://www.empower.org.nz
B. 6 Month Evaluation APS-I (Perheentupa)

- Carry written warning of disease symptoms/complications
- If Howell-Jolly bodies on smear, ultrasound spleen
- Asplenic patients need meningococcal and hemophilus influenza type b immunization and pneumococcal vaccine with measured response. If no response to pneumococcal vaccine, prophylactic daily antibiotics
- Keratoconjunctivitis: Topical steroid and vitamin A
- Potential immunosuppression for hepatitits, refractory diarrhea and other refractory disorders
## Check List APS-I Visit

<table>
<thead>
<tr>
<th>New Symptoms History</th>
<th></th>
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<tbody>
<tr>
<td>New Signs Physical</td>
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<tr>
<td>Oral Candidiasis</td>
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</tr>
<tr>
<td>New Antibodies (21-OH, GAD, IA-2)</td>
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</tr>
<tr>
<td>Ca, Pi, Mg</td>
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</tr>
<tr>
<td>Na, K</td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td></td>
</tr>
<tr>
<td>ACTH, TSH, (LH, FSH)</td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td></td>
</tr>
<tr>
<td>Blood Smear (Howell-Jolly)</td>
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<tr>
<td>Platelet Count</td>
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</tr>
<tr>
<td>Other</td>
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</table>
Oral Cancer Prevention APS-I

- **Aggressive Therapy Oral Candidiasis**
  - Amphoteracin Lozenges for early infection
  - Fluconazole/Keotoconazole (2-3 weeks)
  - Itaconazole (4-6 months) for nail candida

- **Prompt biopsy of suspicious oral lesion**
Immunodeficiency APS-I

- Live virus vaccination avoided
- If splenic atrophy present (Howell-Jolly bodies of blood smear, ultrasound)
  - Pneumococcal vaccine with Antibody response monitoring (6-8 weeks)
  - If no antibody response daily antibiotic prophylaxis
Gastrointestinal disease

- Pernicious anemia
- Autoimmune hepatitis
- Diarrhea
  - Hypocalcemia from hypoparathyroidism
  - Celiac disease
  - Intestinal infection (candida)
  - Autoimmune destruction of endocrine cells of duodenal mucosa
- Severe constipation
Table 8.5
Unusual manifestations of disease – APS-I

- Pituitary hormone deficiency (diabetes insipidus, growth hormone, gonadotropic, ACTH deficiency)
- Autoimmune disease (hyperthyroidism, rheumatoid arthritis, Sjogren’s syndrome, periodic fever with rash, antisperm autoimmunity, hemolytic anemia)
- Hemetologic manifestations (pure red cell aplasia, autoimmune hemolytic anemia, splenomegaly and pancytopenia, Ig A deficiency)
- Ocular disease (iritocyclitis, optic nerve atrophy, retinal degeneration)
- Other organ system involvement (nephritis, cholelithiasis, Bronchiolitis obliterans organizing pneumonia, Lymphocytic myocarditis)
- Hypokalemia with or without hypertension
- Metaphyseal dysostosis
XPID: X-linked polyendocrinopathy, immune dysfunction and diarrhea

- **Other Names**
  - IPEX: Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked
  - XLAAD: X-Linked Autoimmunity Allergic Dysregulation

- **Foxp3 Gene Mutation**

- **Loss of Regulatory T Lymphocytes**
  Bone Marrow Transplant with Chimera “Cures”
  Scurfy Mouse and Man
Mutations for XPID Syndrome
Scurfy/Foxp3/JM2 Gene

Zn = Zinc-finger domain, Zip = Zip Motif
ORF = Predicted Open Reading Frame

Modified from Review by Patel, JCI, 2000
## Type II Syndrome Diseases

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<thead>
<tr>
<th>Disease</th>
<th>HLA Association</th>
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<tr>
<td>Graves’</td>
<td>DR3, DQ2</td>
</tr>
<tr>
<td>Type 1A DM</td>
<td>DR3,DQ2; DR4,DQ8</td>
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<tr>
<td>Celiac</td>
<td>DQ2 (DR5/7 or DR3) and DR4,DQ8</td>
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<tr>
<td>Addison’s</td>
<td>DR3,DQ2; DR4,DQ8</td>
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<tr>
<td>Thyroiditis</td>
<td>DQB1<em>0201; DQA1</em>0301</td>
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<tr>
<td>Insulin Autoimmune</td>
<td>DR4, DRB1*0406</td>
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</table>
Addison’s: DR3/4 DQ8 DRB1*0404

U.S. Odds Ratio: 3/4 DQ8 = 32; 3/4 DQ8 DRB1*0404 = 98

U.S. Risk = 1/200 Addison’s with 3/4 DQ8 DR0404 (1/500 Norway)

Information from Yu et al JCEM, 84:328-335, Myhre et al JCEM, 87:618-623, 2002
PTPN22 Lymphoid Tyrosine Phosphatase R620W Allele in Graves’ and Addison’s Disease

Odds ratio T allele Graves=1.88
Odds ratio T Addison’s=1.69

Velaga et al The codon 620 Tryptophan Allele of Lymphoid Tyrosine Phosphatase (LYP) Gene is a major determinant of Graves’ Disease JCEM 89:5862, 2004
MIC-A
MHC Class I Chain-related Genes

• Near HLA B
• No Classical Binding Groove
• Predominantly expressed in intestine
• NK cell Receptor; gamma delta cells
• Addison’s Association Sanjeevi et al.
• Triplet repeat within gene, and allele 5.1 has 1 extra nucleotide=frameshift, no transmembrane

BDC
JO30 G: Odds ratio 1.5 for combined
Percent 21-OH Autoantibody Positive/ Patients with type 1 DM

N=208                   53                       57             55                      307

Yu et al, JCEM, 1999
21-Hydroxylase Autoantibodies

Levels of autoantibodies

Yu et al, JCEM, 1999

Figure 2

Yu et al, JCEM, 1999

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<thead>
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<th>Stage</th>
<th>ACTH</th>
<th>Cort 0</th>
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</table>
Serositis


- Retrospective review of 20 pts presenting with serositis and autoimmune endocrinopathies between 1967 and 1984 at Vanderbilt University
- Could include: Thyroiditis, Grave’s, Addison’s, 1° hypogonadism, Type 1 DM, 1° Hypoparathyroidism
- Serositis = idiopathic pleuritis, pleural effusion, pericardial effusion, peritonitis or ascites
- Checked Abd: microsomal, thyroglobulin, TSH receptor, islet cells, adrenal cortical cells and ovarian follicular cells
- Extensive Rheumatologic tests
- Immunogenetic tests (HLA antigens)

*Tucker WS. Medicine. 1987.*

Adochio slide
Serositis

Results:

- 7 pts with APS-II
- 4 pts with SLE (?)
- No pt with hypopara or candidiasis
- 45 total episodes of serositis
- 25 episodes in the hospital = 10% of all inpatient cases of idiopathic/rheumatologic serositis
- 4 episodes of pericardial tamponade
- Fevers, pleuritis, dyspnea, pericarditis
- Some episodes occurred simultaneously with onset of endocrinopathy

Adochio slide
Serositis

15 unrelated Caucasian pts:
• 80% HLA-B8 (17% controls)
• 73% HLA-DR3 (22% controls)

17 pts phenotyped for C4:
• 52% C4AQ0 phenotype (all B8 & DR3)

Adochio slide
A family of diseases occurring in families

Type 1A Diabetes
Celiac Disease
Addison’s Disease
WHICH HLA LOCI ARE INVOLVED APS-II?

Modified from Noble
Major DR/DQ Associations

- **Type 1 Diabetes**
  DR3: DRB1*0301/DQA1*0501/DQB1*0201
  DR4: DRB1*0401/DQA1*0301/DQb1*0302

- **Celiac Disease**
  The same as Type 1 DM plus
  DR5/DR7 = DQA1*0501/DQB1*0201 in trans

- **Addison’s Disease**
  The same as Type 1 DM
  but DRB1*0404 preference
  *(Yu, JCEM 84:328, 1999)*
<table>
<thead>
<tr>
<th>DISEASE</th>
<th>INITIATOR</th>
<th>ASSOCIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac</td>
<td>Gliadin/wheat gluten</td>
<td>Predominant</td>
</tr>
<tr>
<td>Insulin AutoImmune</td>
<td>SH-Drugs methimizole</td>
<td>Predominant</td>
</tr>
<tr>
<td>Type 1 DM</td>
<td>Cong Rubella</td>
<td>Rare</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Iodine</td>
<td>“Common”</td>
</tr>
<tr>
<td>Graves’</td>
<td>Anti-CD52</td>
<td>Rare</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>Penicillamine</td>
<td>Rare</td>
</tr>
</tbody>
</table>
IL-21 drives secondary autoimmunity in patients with multiple sclerosis, following therapeutic lymphocyte depletion with alemtuzumab (Campath-1H)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mediator/Autoantigen(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’</td>
<td>Antibody TSH Receptor</td>
</tr>
<tr>
<td>Myasthenia</td>
<td>Antibody ACh Receptor</td>
</tr>
<tr>
<td>Insulin Auto</td>
<td>Antibody Insulin</td>
</tr>
<tr>
<td>Celiac</td>
<td>? Transglutaminase</td>
</tr>
<tr>
<td>Type 1 DM</td>
<td>T Cell Insulin/GAD/ICA512</td>
</tr>
<tr>
<td>Addison’s</td>
<td>T Cell 21-OH</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>T Cell Thyroglobulin Peroxidase</td>
</tr>
</tbody>
</table>
Celiac Disease

- Intestinal Autoimmune Disorder
- Anti-Transglutaminase (EMA)
- 1/200 General Population U.S./Europe
  1/20 Patients with Type 1 DM
  1/6 Patients Type 1 DM who are DR3/DR3
- Gliadin Induction
- Hypothesis: transglutaminase + gliadin
Celiac disease introduction

• Also known as “gluten sensitive enteropathy”
• Celiac disease is considered an autoimmune disease, mediated by T cells
• Associated with other autoimmune diseases
  – Type 1 diabetes, autoimmune thyroid
• Autoantibodies to tissue transglutaminase are one of the hallmark features of celiac disease
Celiac disease introduction

- Gluten is the environmental trigger
  - Comes from a group of plant storage proteins called prolamins
    - Found in wheat (gliadin), rye (secalin), and barley (hordien)
  - Treatment is lifelong dietary avoidance of gluten (gluten-free diet, GFD)
    - Found in pastas, bread, most marinated meats, salad dressings, beer
A brief historical perspective

Early 19th century Dr. Mathew Baillie described a chronic diarrheal disorder causing malnutrition characterized by a gas-distended abdomen. “Some patients have appeared to derive considerable advantage from living almost entirely upon rice.”

75 years later Samuel Gee sensed that “if the patient can be cured at all, it must be by means of diet.” Described a child “who was fed upon a quart of the best Dutch mussels daily, throve wonderfully, but relapsed when the seasons for mussels was over.”

1918 Sir Frederick Still, Royal College of Physicians "Unfortunately one form of starch which seems particularly liable to aggravate the symptoms is bread. I know of no adequate substitute."

1924 Haas Cornerstone of therapy: the high-banana diet. Specifically excluded bread, crackers and all cereals. Decades of success.

Professor Dicke 1950 Bread shortages in Netherlands coincided with improvements in children with celiac disease. When Allied plans dropped bread into the Netherlands, they quickly deteriorated. Doctoral thesis reported that celiac children benefited dramatically when wheat, rye and oats flour were excluded from the diet

1950’s Charlotte Anderson extracted wheat starch and determined that the resulting “gluten mass” was the harmful component of wheat. Formed the basis of today’s “gluten-free diet”
Celiac disease in London, 1938

- diarrhea
- distention
- vomiting
- abdominal pain
- weight loss
- malnutrition
Clinical Presentations

• Intestinal
  – diarrhea, distention, vomiting, abdominal pain, weight loss
• Extra-intestinal
  – rash, pubertal or growth delay, anemia, osteopenia
• Asymptomatic
  – Type 1 diabetes, relative with CD or diabetes
The Celiac Iceberg:

Clinical symptoms 1:5000

Liu
Antibodies and Celiac Disease

- **Anti-Gliadin antibodies** – Less Specific/Less Sensitive ?Utility
- **Calreticulin antibodies** – calcium binding protein
  - Not disease specific
  - No studies to correlate with degree of intestinal injury
- **Anti-actin antibodies** - against cytoskeletal structure
  - Correlation with degree of intestinal injury
  - Needs further study
- **EMA** – Endomysial antibody
  - Immunofluorescent test human umbilical cord
  - Probably = high TG autoantibodies (highly specific/less sensitive)
- **Transglutaminase autoantibodies (TG)**
Diagnosis of celiac disease

Endoscopic findings suggestive of celiac disease (CD) include loss of duodenal folds, scalloped folds.

Normal | Celiac
Histologic Features of CD

Normal

Villous atrophy

IELs
Role of transglutaminase in celiac disease

- **Transglutaminase (TG) is required for:**
  - **Deamidation** of Glutamine (Q) to Glutamic Acid (E) on gliadin peptides
    - Enhances the immunogenicity of gliadin
  - Crosslinks proteins (ie TG-gliadin complexes)
- **Similar to deimination** of arginine to citrulline by peptidylarginine deiminase (PAD) to create citrullinated antibodies in RA and MS
Ovalbumin vs wheat gliadin
Selective deamidation of Glutamine (Q) to Glutamic Acid (E)
QXP into EXP and other algorithms

Proline content ~ 14% of gliadin
Glutamine/Glutamic acid content ~ 46% of gliadin
Significance of TG autoantibodies

- Data controversial, 2 suggest inhibition of enzymatic activity, 2 suggest insufficient inhibition
  - Latest study by Schuppan suggests that patient’s TG autoantibody is insufficient to block TG enzymatic activity
- Pathogenic role?
  - Celiac disease common in selective IgA deficiency
  - No evidence to suggest pathogenic role in enteropathy
Proposed formation of TG autoantibodies

1. TG crosslinks to gliadin
2. Gliadin-TG complexes taken up by B cells
   - Function as a hapten
3. Processed and presented
4. DQ2-gliadin recognized by gliadin-reactive T cell
5. T cell help to B cells to make TG autoantibodies

Adapted from Sollid L, Gut 1997
Population Based Swedish Celiac Cohort
1964-1993: 10,032

<table>
<thead>
<tr>
<th>Age at Death</th>
<th>No. Deaths</th>
<th>Excess Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5-19</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>20-39</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>40-59</td>
<td>828</td>
<td>21</td>
</tr>
<tr>
<td>60-69</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>&gt;=70</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Peters, Arch Int Med 163:1566-1572
Prevalence of TGA by HLA-DR amongst patients with type 1 DM, relatives of DM patients and general population
Higher TG levels are more predictive of villous atrophy

(Marsh Score) Increasing villous atrophy

DGP antibodies resolved sooner than TG on GFD (mean follow-up was 2 years)
Clinical Features of Children With Screening-Identified Evidence of Celiac Disease
Hoffenberg et al, Pediatrics 113:1254, 2004

- 13/18 (2.3-7.3 years old) of Transglutaminase autoantibody+ abnormal small bowel biopsy
- Decreased Z-score weight for height (-0.3)
- Decreased BMI Z-score (-0.3)
- Zinc concentration inversely correlated with intestinal biopsy
- Post antibody increased symptoms (irritability/lethargy; distention/gas; poor weight gain)
Bone Mass Subclinical Celiac Disease
Corazza Bone 18:525, 1996

Median age 28.5, 7/11 relatives CD

Before Gluten Free Diet
The role of HLA-DQ8 57 polymorphism in the anti-gluten T-cell response in coeliac disease

Zaruhi Hovhannisyan, Angela Weiss, Alexandra Martin, Martina Wiesner, Stig Tollefsen, Kenji Yoshida, Cezary Ciszewski, Shane A. Curran, Joseph A. Murray, Chella S. David, Ludvig M. Sollid, Frits Koning, Luc Teyton & Bana Jabri
Celiac Disease

Antigen is a gliadin, a proline/glutamine rich protein in wheat, barley and rye. There are several gliadins, which combine with glutenins to form gluten, the crosslinked elastic protein which allows bread to rise.

All gliadin-specific CD4 T cells from the intestines of adult patients see an immunodominant gluten peptide on HLA-DQ2 or HLA-DQ8. MHC →40% of risk.

The immunogen studied here is α2 gliadin 219-242: QQPQQQQYPSGQGSFQPSQQNPQAQ

From which the epitope (DQ8-α-I) recognized by many HLA-DQ8-restricted CD4 cells is: QGSFQPSQQ “Q” while most see a deamidated version, EGSFQPSQE “E” [Gln 229 and 237 are targets of tissue transglutaminase.]

J COHEN
Tissue Transglutaminase (TG2) is activated during gut inflammation, and converts many gliadin Q residues to E.
From Fig 4 of:
A structural and immunological basis for the role of human leukocyte antigen DQ8 in celiac disease.
Previous/Supplemental: Can get strong responses to native peptides that cannot be demonstrated to bind to HLA-DQ8!
They should have a negative charge to bind to the strongly positive P9 pocket in DQ8. But they don’t.

Can these peptides can be stabilized in the MHC Class II cleft if the TCR has a negative amino acid at CDRβ3 position 3?
Conclusions and speculation:
1. Because of high glutamine (Q) and proline (P) content, gluten peptides are difficult to digest fully, so immunogenic peptides may linger.
2. If absorbed, they associate poorly with HLA-DQ8 because its positive P9 pocket interacts weakly with their uncharged Q.
3. However, the structure of the peptide – DQ8 complex can be stabilized by a TCR with a negative amino acid in CDR3β position 3.
4. Most responsive clones respond as well or better on deamidated peptides where Q → E.
5. TTG is activated in inflammation, causing more Q → E.
6. T cell clones responding to deamidated peptides have no special restrictions on CDR amino acids, so many more clones are recruited.
7. So things go from bad to worse.
Barbara Davis Center

• **New Onset Patients**
  Anti-Islet Autoantibodies
  ½ Hispanic/African American Children not 1A

• **All type 1A patients**
  periodic TSH, transglutaminase and 21-OH Abs

21-OH autoantibody positive: Annual ACTH, cortrosyn

Tg+: Biopsy when level >0.5: Diet Rx if + Biopsy
Demyelinating Neuropathy in Diabetes Mellitus


CIDP: Chronic Inflammatory Demyelinating Polyneuropathy

- Sensory symptoms, limb weakness, pain, poor balance (Type 1 and Type 2 DM)
- Conduction block, prolonged distal motor latency, slowed conduction, delayed or absent F waves
- Odds ratio 11 fold re diabetes present with CIDP than other neurologic disorders
- Treatment response to IV immunoglobulin
Disruption of Intestinal Motility by a Calcium Channel-Stimulating Autoantibody in Type 1 Diabetes

Jackson, Gordon, Waterman Gastroenterology 2004:126:819

• “Functional” autoantibody bioassays in vitro and in vivo (note also Narcolepsy-cholinergic: Lancet 2004:364)

• Type 1 DM: 8/16 patients: Antibodies (Protein A Purified) mouse colon and vas deferens

• L-type channel Voltage Gated Calcium Channels apparent target (block DHP-dihydropyridine antagonist)

• Clinical GI Correlates: Unknown