Current Trends in Celiac disease

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March 12, 2010

History of Celiac Disease

- **Aretaeus, the Cappadocian**
  - Second century
  - "Celiac Affection"
  - From Greek "κοιλιακός" (koiliakos)
  - Malabsorptive syndrome with chronic diarrhoea
  - "lack of heat in the stomach necessary to digest food"

- **Samuel Gee** - British physician - London, 1887
  - Modern description of Celiac disease
  - "if the patient can be cured at all, it must be by means of diet.”

- **Christian Archibald Herter** - American physician
  - In 1908 noted growth retardation in children with celiac disease “intestinal infantilism”
  - Fat was better tolerated than carbohydrate

- **Willem Karel Dicke** - Dutch Pediatrician
  - Noted that death rate of children affected by CD dropped from 35% to <1% during the shortage of bread in 1944 Dutch famine
  - With the availability of wheat mortality rate soared to previously high levels

Celiac disease

- Immune-mediated enteropathy triggered by inappropriate and permanent sensitivity to ingested gluten and gluten like proteins found in wheat, rye and barley

- Limited to individuals with genetic susceptibility
  - Presence of HLA DQ2 or DQ8 on chromosome 6
  - Membrane receptors involved in preferential antigen presentation to CD4+ T cells

Epidemiology

- Estimated to affect 1% of the general population in countries where population is predominantly of European descent
  - In US, prevalence between 2.5-15 years is 3-13 per 1000 (1:300 – 1:80)
  - Incidence in Europe 0.025-3.52 per 1000 live births

- An increased frequency is found in at risk groups:
  - Family members with celiac (10-20% first degree relative)
  - Autoimmune disorders (eg, Type 1 diabetes or autoimmune thyroiditis)
  - Down syndrome, Turner's syndrome, IgA deficiency
Prevalence of Celiac Disease

Celiac disease autoimmunity – (Unpublished – Fasano et al)

1:502

1:219

1:105

n=3,511

n=2,845

n=1,666

1:56

1:133

Presence of Clinical Symptoms and Celiac Disease among first and second degree relatives


<table>
<thead>
<tr>
<th>Group</th>
<th>Symptomatic Cases</th>
<th>Asymptomatic Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relatives</td>
<td>2715</td>
<td>10</td>
</tr>
<tr>
<td>Second degree relatives</td>
<td>1255</td>
<td>310</td>
</tr>
<tr>
<td>Not at risk</td>
<td>306</td>
<td>631</td>
</tr>
</tbody>
</table>

Asymptomatic cases in at risk group have similar prevalence when compared to the symptomatic cases

Multicenter study on sero-prevalence of Celiac Disease in the United States

13,145 Subjects

4,508 First degree 1:22

1,275 Second degree 1:39

3,236 Symptomatic 1:156

4,126 Not at risk 1:133

Common associated conditions

<table>
<thead>
<tr>
<th>Celiac Disease Associated Conditions</th>
<th>Autoimmune conditions</th>
<th>Genetic conditions</th>
<th>Other conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes (4%-8%)</td>
<td>Down syndrome (5%-8%)</td>
<td>Turner Syndrome</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Thyrotoxicosis (6%)</td>
<td>Down syndrome (5%-8%)</td>
<td>Turner Syndrome</td>
<td>Psychologic</td>
</tr>
<tr>
<td>Rheumatoid arthritis (3%)</td>
<td>SLE (5%)</td>
<td>Turner Syndrome</td>
<td>Aplasia</td>
</tr>
<tr>
<td>Primary biliary cirrhosis (6%)</td>
<td>SLE (5%)</td>
<td>Turner Syndrome</td>
<td>Depression</td>
</tr>
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</tbody>
</table>

Clinical presentation

<table>
<thead>
<tr>
<th>Onset of symptoms as early as 6 months</th>
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</thead>
<tbody>
<tr>
<td>Untreated Celiac Disease in Pediatric patients</td>
</tr>
<tr>
<td>Classic symptoms</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Abdominal distention</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Chronic or recurrent diarrhea</td>
</tr>
<tr>
<td>Failure to thrive or weight loss</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
<tr>
<td>Muscle wasting</td>
</tr>
<tr>
<td>Dermatitis herpetiforms</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Anorexia</td>
</tr>
<tr>
<td>Chronic or recurrent diarrhea</td>
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</table>

Dermatitis Herpetiformis

- 1966 Dermatitis herpetiformis was linked to celiac disease
- 10% of adults with celiac disease (25-45 year)
- Uncommon in pediatric patients
- Intestinal lesions are usually less severe


Screening - Serology

- Antigliadin antibody (AGA) IgA and IgG has a low sensitivity and has not been recommended in testing for Celiac disease by NASPGHAN and NIH
  - Present in 80-90% of untreated Celiac
  - False positive: esophagitis, gastritis, gastroenteritis, IBD, cystic fibrosis, cow’s milk protein intolerance, liver disease and neurological conditions
  - "Serologic testing for celiac disease in children less than 5 years of age may be less reliable and requires further study. NIH consensus on Celiac disease"

Screening - Serology

- Deamidated AGA antibody recognizes gliadin after TTG deamination process (DGP more specific then AGA) IgG
- Tissue transglutaminase antibody (TTG IgA and IgG)
- Anti-endomysium IgA (EMA)

Screening - Serology

Efficacy of serology testing in children less then 3 years

- 116 children with clinical signs of celiac disease and positive family history
- All underwent endoscopy with biopsies and serological testing


Median concentration of CD specific antibodies in biopsy positive children

<table>
<thead>
<tr>
<th>No. of children</th>
<th>≤3 years</th>
<th>&gt;3 years</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA (mg/dL)</td>
<td>86.8</td>
<td>121.0</td>
<td>0.045</td>
</tr>
<tr>
<td>TTG IgA (U/mL)</td>
<td>0.91</td>
<td>10.9</td>
<td>0.066</td>
</tr>
<tr>
<td>EMA (reciprocal of end point titer)</td>
<td>160</td>
<td>160</td>
<td>0.182</td>
</tr>
<tr>
<td>DGP (IgG-IgA)</td>
<td>28.0</td>
<td>8.5</td>
<td>0.000</td>
</tr>
<tr>
<td>TTG IgA (U/mL)</td>
<td>95.9</td>
<td>61.8</td>
<td>0.000</td>
</tr>
<tr>
<td>EMA*</td>
<td>71.6</td>
<td>42.5</td>
<td>0.398</td>
</tr>
</tbody>
</table>

Performance of Serology Assays for Diagnosing Celiac in a Clinical Setting.
HLA testing

- HLA DQ – 9 serotypes on chromosome 6p21
  - HLA DQ2 - HLA-DQA1*0501 and DQB1*02 alleles
  - HLA DQ8 - HLA-DQA1*0301-DQB1*0302 alleles
- 90-99% of Celiac have DQ2 or DQ8
- 90-95% with DQ2 and 5-10% with DQ8
- 35-45% of US population have DQ2 or DQ8
- At most 1% of population suspected of having celiac
  - Other genetic factors

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Screening ↔ Diagnosis

- Endoscopy with biopsy is required to confirm serological diagnosis of Celiac disease
  - 6 to 8 random biopsy specimens from the duodenum or further
  - Except in biopsy proven dermatitis herpetiformis

- Patchiness in 73%
- At least one normal appearing fragment - 36%
  - Emphasis on obtaining biopsies from the duodenal bulb in addition to other random small bowel sites

Endoscopic biopsies in the evaluation of celiac disease

- Marsh 0: Normal mucosa and villous architecture, IELs
- Marsh 1: Hyperplastic: + enlarged crypts, increased turnover, normal villi, IELs
- Marsh 2: Destructive lesion with IELs: A. partial VA, B. sub-total VA, C. total VA
- Marsh 3: Hyperplastic: + enlarged crypts, increased turnover, normal villi, IELs
- Marsh 4: Infiltrative Normal mucosa and villous architecture, IELs

Pathology scores

Capsule endoscopy

- Features suggestive of celiac disease: villous atrophy, Scalloping, Fissuring, Mosaic patterns
- No tissue samples

Treatment

GFD (Gluten Free Diet)

- Avoid wheat, rye, barley and their derivatives
- Malt is also harmful - partial hydrolysate of barley prolamins
- Oats – High incidence of cross contamination
- FDA definitions of FGD <20ppm (<20mg/kg)
- Improved carbohydrate intolerance
Gluten containing grains

- Barley
- Barley malt/extract
- Bran
- Bulgur
- Couscous
- Bromated or Durum Flour
- Einkorn
- Emmer
- Enriched or Self Rising Flour
- Farina
- Faro
- Graham Flour
- Kamut
- Matzo Flour/meal
- Orzo
- Panko
- Phosphated Flour
- Rye
- Seltan
- Semolina
- Spelt
- Triticale (cross between wheat/rye)
- Udon
- Wheat
- Wheat Bran
- Wheat germ
- Wheat starch

Gluten free grains and starches

- Amaranth
- Arrowroot
- Buckwheat
- Corn
- Flax
- Millet
- Montina
- Potato Starch
- Potato Flour
- Flours made from nuts, beans and seeds
- Quinoa
- Rice
- Rice Bran
- Sago
- Sorghum
- Soy (soya)
- Tapioca
- Tef

Benefits of strict dietary compliance

- Eliminate immunological damage
- Improve nutrition, vitamin absorption
- Growth, bone mineralization
- Physical and psychosocial well being
- No consensus on the minimal amount of gluten in food
- Patient reported adherence to GFD – 45-81%
- Serological monitoring every 6-12months
- No increase in mortality compared to general population

Consequence of Non Compliance

- Increased chance of developing other immune mediated conditions (Autoimmune diseases)
- Increased lifelong incidence of malignancy
  - If diagnosed and treated in childhood, lifelong risk of gastrointestinal lymphoma is not higher than general population
- Mortality rate*
  - Double in patients suspected on non compliance
  - X6 in patients not on diet

*Mortality

- Early diagnosis in pediatric patients associated with decreased mortality
- Increased gluten consumption
- Lymphoma

Mortality

Can bacterial or viral infection trigger the onset of celiac disease?

- The association of celiac disease with adenovirus (serotype 12) *
  - Viral protein- Elb demonstrates similar antigenic sequencing of amino acids to that of gluten peptides
  - Infection with adenovirus and subsequent exposure to gliadin could trigger the development of cross-reacting immune response
- Welander et al. (2/2010)** looked at nearly 10,000 children in Sweden and showed no increased incidence of future celiac disease development in children exposed to gluten during the time of infectious illness

New Therapeutic Strategies

- Genetic alterations to remove or modify immunogenic sequences
  - Interferes with the main structural role in maintaining protein matrix in the grain
  - Interferes with the dough strength
- Selection of grains with low or absent immunogenic sequences
- Polymeric binders to reverse gliadin effect on the intestinal barrier


New Therapeutic Strategies

- Enzymatic degradation of gluten prior to ingestion
  - Enzymes used during food preparation and storage
  - Probiotics to degrade gluten into less immunogenic form
    - VSL3 was shown to hydrolyze gliadin peptide responsible for mucosal immune response
  - Inhibition of intestinal permeability
    - AT1001 (1002) blockage of tight junction relaxation leading to paracellular permeability


New Therapeutic Strategies

- Blocking TTG
  - Interferes with deamidation of gluten by TTG
  - Decrease immune response
  - Potentially harmful since TTG has a role in apoptosis, cell adhesion, signal transduction, collagen assembly and would repair
- Blocking HLA DQ groove
  - Single amino acid substitution of a gliadin can abolish immunogenicity of a T cell response
- Shifting from Th1 to Th2 response
  - Inhibiting inflammation
  - Nematode infection (Australia)


New Therapeutic Strategies

- Anti-inflammatory cytokines
  - Human recombinant - IL10 suppresses gluten dependent T activation in cultured cells
- Gluten peptide vaccine
  - Peptide that combines two immunodominant α and ω-gliadin 17-mer peptides is currently under investigation
- Inhibition by dietary Antigen specific T regulatory cells (Type 1)
  - Shown to inhibit pathogenic T cells
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- Inhibition by dietary Antigen specific T regulatory cells (Type 1)
  - Shown to inhibit pathogenic T cells


New Therapeutic Strategies

- Gluten tolerance induction in high risk infants
  - Currently under investigation in Europe in children 4-7 months of age
  - Promising results in DQ8 transgenic mice
- Anti adhesion therapy
  - Selective inhibition of leukocyte adhesion
- Intestinotrophic mitogens
  - Stimulation of intestinal growth and regeneration (R-spondin 1, KFG)

And the Winner is:

GFD

With COMPLIANCE

Questions?