Celiac disease:
All that you need to know

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Disclosures

• No disclosures in relation to this presentation
How common is Celiac Disease?
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>West</td>
<td>2003</td>
<td>UK</td>
<td>1.2%</td>
</tr>
<tr>
<td>Sanders</td>
<td>2003</td>
<td>UK</td>
<td>1%</td>
</tr>
<tr>
<td>Vilppula</td>
<td>2009</td>
<td>Finland (adults 52-74)</td>
<td>2.1%</td>
</tr>
<tr>
<td>Mylers</td>
<td>2009</td>
<td>Sweden (Children born 1984-96)</td>
<td>3%</td>
</tr>
<tr>
<td>Greco</td>
<td>2011</td>
<td>Near and Middle East</td>
<td>0.5-1.3%</td>
</tr>
</tbody>
</table>
UK

- General population sample: n = 7550
- Age 45-76
- EMA positive - 1.2%
  - More likely to report “good or excellent” health
  - Lower
    - Weight
    - Cholesterol
    - Hb
    - Total protein
    - Corrected calcium
  - More
    - Osteoporosis
    - Mild anemia
  - Fewer
    - Smokers

US

- 3850 adult residents of Natrona County, Wy
  - 0.8% TTG +
    - 1.5% 18-30.
- Symptoms associated with positive serology
  - Feeling full (46 %)
  - Heartburn (40 %)
- Of symptomatic subjects:
  - 11 complained of constipation,
  - 5 reported diarrhea
  - 2 had a family history of celiac disease.
- Conversely, 44 % of those who underwent biopsy were asymptomatic

How does it present?
Clinical Presentations

- **Classical**
- **Common**
  - 7:1 = Latent:Overt
- **Associated conditions**
  - DH
  - DM
  - Other endocrine disorders
  - Down’s syndrome
  - Autoimmune disorders
- **Atypical**
Presenting symptoms of coeliac patients 1991-2001

n = 260

Diarrhoea/Abdo pain/Wt loss
Anaemia
Screening
Oral ulceration
Vomiting
Abnormal LFTs
DH
Recurrent abortions
Amenorrhoea

O’Leary C. 2003
Patient Support Group USA

- N= 1032
- Median age at onset - 46
- Interval to Dx - 12 months
- Underweight - 32%
- Frequent diarrhoea - 50%

<table>
<thead>
<tr>
<th>Presenting Symptoms</th>
<th>Initial Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue 82%</td>
<td>IBS 37%</td>
</tr>
<tr>
<td>Abdo pain 77%</td>
<td>Psych 29%</td>
</tr>
<tr>
<td>Bloat/Gas 73%</td>
<td>Fibromyalgia 9%</td>
</tr>
<tr>
<td>Anaemia 63%</td>
<td></td>
</tr>
</tbody>
</table>

Associated Conditions

- Dermatitis herpetiformis
  - 100% have CD
- Diabetes
  - 2-9%
- IgA deficiency
  - Incidence X 10
- Other endocrine disorders
  - Autoimmune thyroid disease: 4.3%
  - Infertility (female and male)
  - Miscarriages
  - Delayed menarche, premature menopause
- Down’s and Turner’s syndromes
- Autoimmune disorders
  - Prevalence related to duration of gluten exposure
  - Sjogren’s: 15%
Atypical Presentations

- Abnormal LFT’s, Liver Disease
- CNS
- Metabolic bone disease
- Microscopic/lymphocytic/collagenous colitis and gastritis
- IBS
The Liver and Coeliac Disease

- PBC
- PSC
- Autoimmune Hepatitis
- Autoimmune cholangiopathy
- NASH

- CD as a cause of elevated transaminases
  - RR CD in unexplained hypertransaminasemia = 18

Neurological Manifestations

- Epilepsy
  - 0.79-5%
  - Cerebral calcification and folate deficiency
  - 1 in 44 at a seizure clinic
    - Cronin CC, et al. QJM 1998;91:303-8
- Migraine
- Myoclonus
- Internuclear ophthalmoplegia
- Multifocal leucoencephalopathy
- Dementia
- Schizophrenia
- Peripheral neuropathy
- Ataxia

  - Most anecdotal; need prospective epidemiological studies

Wills AJ. Neuropathol Appl Neurol 2000;26:493-6
Cerebellar Ataxia

- 104 patients with sporadic cerebellar ataxia
- 12 had positive antibodies (mostly AGA)
- 2 had classical CD histology; 5 had increased IEL’s

Diagnosis
Diagnosis

- **Serology**
  - AGA
  - EMA
  - TTG
  - HAL
- **Radiology**
  - Non-responsive disease
- **Endoscopy**
- **Biopsy**
## Serology and HLA

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Predictive Value (%)</th>
<th>Likelihood Ratio (%)</th>
<th>Posttest Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>56</td>
<td>97</td>
<td>43/98</td>
<td>21/0.45</td>
<td>43/1.6</td>
</tr>
<tr>
<td>TTG</td>
<td>81</td>
<td>99</td>
<td>76/93</td>
<td>91/0.19</td>
<td>76/0.67</td>
</tr>
<tr>
<td>EMA</td>
<td>81</td>
<td>99</td>
<td>76/93</td>
<td>91/0.19</td>
<td>76/0.67</td>
</tr>
<tr>
<td>HLA-DQ2</td>
<td>94</td>
<td>73</td>
<td>11/100</td>
<td>3.5/0.085</td>
<td>11/0.3</td>
</tr>
<tr>
<td>HLA-DQ8</td>
<td>12</td>
<td>81</td>
<td>2.3/96</td>
<td>0.66/1.1</td>
<td>2.2/3.7</td>
</tr>
<tr>
<td>HLA + Serology</td>
<td>81</td>
<td>98</td>
<td>59/99</td>
<td>40/0.19</td>
<td>59/0.68</td>
</tr>
</tbody>
</table>

**Bottom Line**

TTG/EMA excellent diagnostic tests
HLA typing to exclude Celiac disease

Endoscopy in Coeliac Disease

- Non-specific
- Observer-dependent
Pathology

• **Marsh Classification:**
  - 0: pre-infiltrative
  - 1: Infiltrative. Increased IEL’s only. 40% DH, 10% of CD relatives
  - 2: Hyperplastic. Increased IEL’s + Villous/Crypt ratio < 3:1
  - 3: Destructive (CLASSICAL: PVA/SVA/TVA)
  - 4: Hypoplastic. Collagen deposition, non-responsive.
Subclinical Sprue
- Atypical Symptoms
- Positive Serology
- Diagnostic Biopsy

Silent Sprue
- Asymptomatic
- Positive Serology
- Diagnostic Biopsy

Potential Sprue
- May be symptomatic
- Positive Serology
- Non-diagnostic Biopsy

Classical Sprue
- Typical Symptoms
- Positive Serology
- Diagnostic Biopsy

Latent Sprue
- Asymptomatic
- Positive Serology
- Normal Biopsy
ESPGHAN Criteria 1990

1. History and clinical presentation compatible with celiac sprue
2. Positive serology
3. Compatible histology
4. Clinical and serological response to GFD
5. Over 2 years of age
6. Other conditions mimicking CD excluded
Group 1: children with symptoms suggestive of CD
- Diagnosis based on symptoms, positive serology, and histology.
- If IgA TTG titers are high (>10 times ULN), can diagnose CD without biopsy by applying a strict protocol with further laboratory tests.

Group 2: asymptomatic children at increased risk for CD
- Diagnosis of CD based on positive serology and histology.

HLA-DQ2 and HLA-DQ8 testing valuable because CD is unlikely if both haplotypes are negative.

Can we avoid histology?

Yes

- If typical symptoms
- If TTG and EMA positive
- Will predict “classical” histology

Other causes of Villous Atrophy in adults

Pathologic findings characteristic but not diagnostic
- Tropical Sprue
- Adult-onset autoimmune enteropathy
- Hypogammaglobulinemia
- Idiopathic AIDS enteropathy

Pathologic findings could be diagnostic
- Eosinophilic gastroenteritis
- Whipple's disease
- Abetalipoproteinemia
- Intestinal lymphoma
- Collagenous sprue
- Tuberculosis
- Giardiasis
- Crohn's disease

Pathologic findings non-specific
- Small-bowel bacterial overgrowth
- Infectious enteritis
- Parasitic infestation
- Severe malnutrition
- Small-bowel ischemia
Outcome
Response to GFD

• 341 patients with follow-up biopsy 5 months to 35 years later.
  – Histological improvement in 45%; mucosal recovery in 37%
    • PVA - 45%
    • TVA - 28%
  – 56% of positive TTGs sero-converted
  – 72% of positive EMAs sero-converted

Response to GFD

• Predictors of persistent mucosal damage:
  – Poor compliance to GFD
  – Severe CD defined by diarrhea and weight loss
  – Total villous atrophy at diagnosis

• Trend toward an association between achievement of mucosal recovery and reduced rate of all-cause mortality

Transition from Child to Adult

- 103 CD patients reevaluated >20 yrs post Dx
- 22% at adult GI clinic
- 50% fully compliant
  - Fear of symptoms
- Fe deficiency:
  - 86% females
  - 21% males
- Osteopenia:
  - 29%

Non-Responsive CD

- Persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet (GFD) for at least 6-12 months in the absence of other causes of non-responsive treated celiac disease (CD) and overt malignancy

- By definition, HLA DQ2 or HLA DQ8 positive

Rubio-Tapia A, and Murray J.A. Gut 2010;59:547-557
Non Responders

- Non-adherence, partial adherence, inadvertent exposure
- SIBO
- Lactose intolerance
- Pancreatic insufficiency
- Lymphocytic/collagenous colitis
- IBS
- True non-responder
Microscopic/Lymphocytic Colitis
Non-Responsive CD

- **Type I**: normal intraepithelial cell phenotype
  - Usually responds to strict GFD, steroids and/or thiopurines

- **Type II**: abnormal (clonal) intraepithelial cell phenotype
  - Ulcerative jejuno-ileitis and ulcerations common
  - No established therapy
  - 5-year survival 40-58%

Rubio-Tapia A and Murray JA. Gut 2010;59:547-557
Complications

- Ulcerative jejuno-ileitis
- Enteropathy-associated T-cell lymphoma (EATL)
- Adenocarcinoma and other malignancies

Rubio-Tapia A and Murray JA. Gut 2010;59:547-557
Malignancy

• Features of concern:
  – Fever, nocturnal diaphoresis, pruritus, significant unexplained weight loss, anorexia, overt or occult gastrointestinal bleeding, abdominal pain, bowel obstruction

• EATL:
  – Type 1 (80–90%)
    • Linked to CD and RCD
    • Non-monomorphic cytomorphology,
    • CD56 negativity,
    • Chromosomal gains of 1q and 5q
    • May occur in 60–80% of RCD Type 2 within 5 years

Rubio-Tapia A and Murray J.A. Gut 2010;59:547-557
Duodenal Adencocarcinoma in CD

GI Cancer in CD

- Villous atrophy (n=28,882), Marsh 1-2 (n=12,860), Latent (n=3705)
- Risk of GI cancer in first year after diagnosis:
  - Hazard ratio: 5.95, 9.13, 8.1
    • Colon, Rectum, Small Intestine, Pancreas
- Risk in subsequent years:
  - 1.07, 1.16, 0.96

Summary

- Celiac disease is common and usually undiagnosed
- The “atypical” presentation now predominates in adults; many are asymptomatic
- Though histology remains the “gold standard”, biopsy may be avoidable in some cases
- Mucosal recovery may be uncommon in adults
- New insights into pathophysiology may open the way to new approaches to therapy