Celiac Disease in Children

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Nationwide Children’s Hospital

Disclosure

I have no relevant financial relationships with the manufacturers of any commercial products and/or provider of commercial services discussed in this CME activity.

I do not intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.
Celiac Disease

Celiac Disease Facts
- Affects ~ 1% of the USA population*
- 2-3 million cases in the USA
- 5-20 affected children in average practice
- ~ 80% undiagnosed

*Arch Int Med 2003;163:286-92
  • Med 2003;163:286-92

Learning Objectives

Identify children in need of testing for celiac disease
Choose most effective serological tests for screening
Understand the need to confirm the diagnosis before treating.
Celiac Disease Guidelines: 2004-2013

Who to test?  How to test?  How to Treat?
### Celiac Disease Guidelines

**Who to test?**

- **Symptomatic**
  - “typical” – first line test
  - “less typical” – consider
Celiac Disease Guidelines

Who to test?

Symptomatic
- “typical” – first line test
- “less typical” – consider

What Symptoms are associated with celiac disease?

Symptomatic CD

Symptoms in children

Highly variable
- age of onset
- severity of symptoms
- single or combined
Symptomatic CD

Symptoms in children

Highly variable
- age of onset
- severity of symptoms
- single or combined

Symptoms mainly GI in young children. Non-GI sx more common later.

Celiac Disease

- Symptomatic group
  - Gastrointestinal – early onset
  - Age – 6 mths – 2 yrs

Abdominal distention
Anorexia
Weight loss
Wasting
Diarrhea
Steatorrhea
Celiac Disease

Symptomatic group
- Gastrointestinal – late onset
- Age – childhood to young adult

Symptoms:
- Transaminitis
- Abdominal Distension
- Constipation
- Anorexia
- Weight Loss
- Nausea
- Vomiting
- Diarrhea
- Steatorrhea
- Pain
- Bloating
- Flatulence

Non-Gastrointestinal
- Skin and mucous membranes
- Dermatitis herpetiformis
- Aphthous ulcers
Celiac Disease

Symptomatic group
Non-Gastrointestinal

Musculoskeletal system
Short stature
Rickets
Osteopenia
Osteoporosis
Arthritis
Fractures

Celiac Disease

Symptomatic group
Non-Gastrointestinal

Hematological system
Anemia
iron deficiency
folate/B12
Leukopenia
Bruising/bleeding
vitamin K deficiency
platelet dysfunction
Celiac Disease

**Symptomatic group**

Non-Gastrointestinal

**Miscellaneous**

- Dental enamel hypoplasia
  - Reproductive system
    - pubertal delay
    - infertility
    - recurrent abortions
    - low birth weight
  - Central nervous system
    - behavioral changes
    - anxiety disorders
    - learning difficulties

**Asymptomatic group**

- At risk for CD
Celiac Disease

### Asymptomatic group
- At risk for CD

<table>
<thead>
<tr>
<th>Autoimmune</th>
<th>Non-autoimmune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 DM</td>
<td>Relatives</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>A.I. Hepatitis</td>
<td>Turner syndrome</td>
</tr>
<tr>
<td>Sjogren’s</td>
<td>Williams syndrome</td>
</tr>
<tr>
<td>Arthritis</td>
<td>syndrome</td>
</tr>
<tr>
<td></td>
<td>IgA deficiency</td>
</tr>
</tbody>
</table>
### Celiac Disease Guidelines

#### Who to test?

<table>
<thead>
<tr>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
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</table>
| - “typical” – first line test  
- “less typical” - consider | - general population - no  
- at risk groups - debate |
Celiac Disease Guidelines

Who to test?

Symptomatic
- “typical” – first line test
- “less typical” - consider

Asymptomatic
- general population - no
- at risk groups - debate

Not so fast!!
Celiac Disease
Testing the Asymptomatic Debate

Protagonists!
- Increased mortality
- Increased malignancies
- Other morbidities
  - bones, growth, other AID’s
Celiac Disease

Testing the Asymptomatic Debate

Protagonists!
- Increased mortality
- Increased malignancies
- Other morbidities – bones, growth, other AID’s

Antagonists!
- Natural history unknown
- Benefits - uncertain
- Compliance - poor
- QOL issues

Celiac Disease Guidelines

Who to test?  How to test?

How to Treat?
Celiac Disease

Commercially available tests

Antigliadin – IgA AGA & IgG AGA

Transglutaminase – IgA tTG (IgG tTG)

Endomysium – IgA EMA (IgG EMA)

Deamidated gliadin – IgA DGP & IgG DGP

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (percent)</th>
<th>Specificity (percent)</th>
<th>Technology</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA AGA</td>
<td>80 (52-100)</td>
<td>85 (47-100)</td>
<td>Low</td>
<td>$</td>
</tr>
<tr>
<td>IgG AGA</td>
<td>80 (42-100)</td>
<td>80 (47-94)</td>
<td>Low</td>
<td>$</td>
</tr>
<tr>
<td>IgA tTG</td>
<td>95 (86-100)</td>
<td>96 (90-98)</td>
<td>Low</td>
<td>$$*</td>
</tr>
<tr>
<td>IgA EMA</td>
<td>90 (86-100)</td>
<td>98 (94-100)</td>
<td>High</td>
<td>$$$$+</td>
</tr>
<tr>
<td>IgA DGP</td>
<td>88 (74-100)</td>
<td>90 (80-95)</td>
<td>Low</td>
<td>$$#</td>
</tr>
<tr>
<td>IgG DGP</td>
<td>80 (70-95)</td>
<td>98 (90-100)</td>
<td>Low</td>
<td>$$#</td>
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JPGN 2012;54:229-241
### Recommended Testing for Celiac Disease.

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*Most reliable and cost effective single test: Need to know serum IgA level?*
Celiac Disease
Special Considerations

IgA deficiency
- IgG (tTG, EMA or DGP)
- consider biopsy

Celiac Disease
Special Considerations

IgA deficiency
- IgG (tTG, EMA or DGP)
- consider biopsy

The young child (< 2 yrs)
- tTG IgA + DGP IgG
  (ESPGHAN)
Celiac Disease

Genetic tests for celiac disease

HLA - DQ2/8
Celiac Disease

Genetic tests for celiac disease

- HLA - DQ2/8
- Non-HLA (39)
Celiac Disease

HLA genes in celiac disease
- DQ2 > 95% of celiac individuals
  20% - 30% general population
- DQ8 majority of non DQ2 cases

DR3-DQ2

DR5-DQ7

DR7-DQ2

DQ2 - inherited in cis

DQ2 - inherited in trans

The Gene Dose Effect*

Relative risk
- DQ2 homozygous
- DQ2 + DQB1*02
- DQ2 + DQ/X

- Increased peptide binding & gluten specific T cell response #

Celiac Disease

- Non DQ2 and/or DQ8 celiac
  - European collaborative study#
  - 1008 biopsy confirmed cases
  - 61 negative for DQ2 and/or DQ8
  - 57 positive for half the DQ2 heterodimer
    - 41 – DQB1*02
    - 16 – DQA1*05

How to use HLA-DQ2/8

- Specific alleles
- Not for diagnosis
- Selective use
Definitive Testing

Celiac Disease
Is a biopsy needed in all cases?

Yes
Yes
Yes
No
Celiac Disease and Beyond

Biopsy Consensus Points

Endoscopic

Multiple Bulb & distal

Normal Scalloping Nodularity Normal Atrophic

Celiac Disease

Normal 0 Infiltrative 1 Hyperplastic 2

Partial atrophy 3a Subtotal atrophy 3b Total atrophy 3c

Celiac Disease

Confirming the Dx

- Marsh III – strong
- Marsh II – moderate
- Marsh I – weak

Celiac Disease

Non Biopsy diagnosis?
### Celiac Disease

#### Non Biopsy diagnosis?

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<td>EMA +ve</td>
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#### Symptomatic + tTG >10x ULN

| EMA +ve                      |
| HLA DQ 2/8                   |
Non Biopsy diagnosis?

Symptomatic
+ tTG >10x ULN

EMA +ve
HLA DQ 2/8

Symptoms resolve
Serology resolves

• Recommendation 3.4.1.
  – Every antibody test must be validated in a paediatric population of at least 50 children with active CD and 100 control children……..
  – Laboratories providing CD antibody test results should participate continuously in quality control programs at a national or European level.
Celiac Disease

Confirming the Dx

Comparison of Commercially Available Serologic Kits for the Detection of Celiac Disease

Afzal J. Ruley, MD, Lincoln Hernandez, MD, Edward J. Clavio, PhD, Konstantinos Papadakis, MD, John E. Manninen, MD, Gordon Blaustein, MD, and Peter B. R. Green, MD

Sensitivity - 71.4 – 96.4%
Specificity - 87.5 – 100%
False + ve - 13 -25%

Diagnostic Accuracy of Ten Second-Generation (Human) Tissue Transglutaminase Antibody Assays in Celiac Disease

Brent Van Meren, MD, Mark Rosen, MD, Martin Hensley, MD, Eduardo Ramon, MD, Konstantinos Papadakis, MD, John E. Manninen, MD, Gordon Blaustein, MD, and Peter B. R. Green, MD

Sensitivity - 71.4 – 96.4%
Specificity - 87.5 – 100%
False + ve - 13 -25%
Celiac Disease

Confirming the Dx

ESPGHAN Guidance on Coeliac Disease 2012: Multiples of ULN for Decision Making Do Not Harmonise Assay Performance Across Centres

*William Egger, Anna Shrimpton, Ravishankar Surgur, Divish Patel, and Kirsty Swallow

ABSTRACT

This updated ESPGHAN guideline on coeliac disease recommends the use of different multiples of the upper limit of normal (ULN) for IgA anti-endomysium antibody (EMA) and IgA anti-tissue transglutaminase (IgA anti-TTG), as well as the use of IgA anti-gliadin (IgA anti-GliA) for a gluten-free diet (GFD) responder. The current consensus is that a person is considered to have coeliac disease if they have a positive test result for IgA anti-TTG and IgA anti-GliA, and a negative test result for IgA anti-GliA, and have been on a strict GFD for a minimum of 3 months. The guideline also recommends that IgA anti-GliA testing should not be used in the absence of a gluten-free diet. The guideline further states that the use of different multiples of ULN for decision-making does not harmonise assay performance across centres, and that more research is needed to determine the optimal multiples of ULN for decision-making.
Celiac Disease

Confirming the Dx

"As a result, the updated guidance is too generalized for use with all commercial TG2 kits and is therefore not translatable for us in all centres."

Celiac Disease

Non Biopsy Dx?
Celiac Disease

Non Biopsy Dx? → Ideal!

Possible? → USA - Not yet!

Treatment for celiac disease

• **Recommendations**
  • Always confirm before treating
  • Confirmation mandates GFD for life
    – Following a strict GFD is not easy
    – Diet has potential QOL implications
  • Failure to treat has potential long term adverse health consequences
    – Increased morbidity and mortality
## Celiac Disease

### Celiac disease - current treatment

- **Strict GFD for Life!**
- **Skilled nutritionist**
  - assessment and education
- **Follow-up**
  - growth/health monitoring
  - serological resolution

### Celiac Disease

### Celiac disease – future treatment?

**Alternatives to the GFD?**
- digestive enzymes
- biologics

**Prevention?**
- infant feeding practices
- vaccines
Celiac Disease

- Resources
- www.gikids.org (click on celiac disease)
- Guidelines for evaluation and management
  - Patient information brochures
  - Start up diet
  - Gluten free drug list

Presentation of Celiac Disease in Adults

Sheryl Pfeil, MD
Associate Professor – Clinical
Department of Internal Medicine
Division of Gastroenterology, Hepatology & Nutrition
The Ohio State University Wexner Medical Center
### Presentation of Celiac Disease in Adults

- Delay in diagnosis common ("celiac iceberg")
- May be diagnosed at any age
- No weight exclusion
- Geographically widespread

<table>
<thead>
<tr>
<th>Presentation of Celiac Disease in Adults</th>
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<tbody>
<tr>
<td>• Frequent cause of unexplained iron deficiency</td>
</tr>
<tr>
<td>• GI symptoms: diarrhea, bloating, &quot;IBS&quot; type symptoms</td>
</tr>
<tr>
<td>• Spectrum of severity and symptoms; majority have mild symptoms; mono- or oligosymptomatic</td>
</tr>
<tr>
<td>• Non-GI manifestations and celiac associated conditions</td>
</tr>
</tbody>
</table>
Celiac Disease and Iron Deficiency in Adults

- 5-8% of adults with unexplained iron deficiency anemia have CD
- Many patients undergoing EGD for anemia do not get duodenal biopsies
- Macroscopic and microscopic findings
- Biopsy duodenal bulb and descending duodenum (2 + 4)

Endoscopic "Clues" in Diagnosis of Celiac Disease

- Loss of duodenal folds
- Fissuring or scalloping along folds
- Nodularity
- Mosaic pattern
Endoscopic "Clues" in Diagnosis of Celiac Disease

Normal Duodenum

Celiac Disease

Endoscopic "Clues" in Diagnosis of Celiac Disease

Capsule Endoscopy in Celiac Disease
Microscopic Diagnosis of Celiac Disease

- Spectrum of change

- "False positive" biopsies (NSAIDs, olmesartan, tropical sprue, autoimmune enteropathy, self-limited enteritis, Crohn's)

- Correlate with serologies and HLA type

Abnormal Liver Tests and Celiac Disease

- Incidental elevated transaminases (ALT, AST): up to 9% may have “silent” celiac disease

- Non-specific reactive hepatitis

- Liver tests normalize on a gluten free diet

- Other associated autoimmune liver disorders
  - Primary biliary cirrhosis
  - Autoimmune hepatitis
## Conditions Associated with Celiac Disease in Adults

- **Dermatitis herpetiformis**
- Cerebellar ataxia
- Arthralgias
- **Osteoporosis**
- Reproductive disorders
- Small bowel malignancies (lymphoma and adenocarcinoma)

### Dermatitis Herpetiformis

- Symmetric pruritic papules and vesicles on forearms, knees, buttocks
- Majority (90%) no GI symptoms
- Majority (75+% have increased IEL's or villous atrophy)
- Gluten sensitive
- Responds to gluten withdrawal

[Image: Dermatitis Herpetiformis symptoms]
Osteopenia and Osteoporosis

- Early fractures often without GI symptoms
- Secondary hyperparathyroidism due to vitamin D deficiency
- Peripheral > axial bone loss
- Partial reversal on gluten free diet
- Perform DXA scan at diagnosis

Treatment of Celiac Disease

- Gluten free diet
- Dietician referral
- Motivation: reduced complications
- Explosion of gluten free food industry

Image is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.

Author: Gérard Loren

The Gluten-free Diet Plate

Author: DryPot
# Early Management of the Adult Celiac Patient

| • Confirm diagnosis before treatment |
| • Diet instruction and support  |
| • Gluten free diet for life  |
| • Avoid wheat, barley, and rye  |
| • Test for (and correct) nutrient deficiencies  |
| • DXA scan to evaluate for bone loss  |

| • Follow response to therapy  |
| • Recheck serology (if initially positive)  |
| • Support group  |
**Late Management of the Adult Celiac Patient**

- Annual visit

- Repeat DXA scan (and vitamin D testing) depending on initial results

- May check serology (if initially positive) and routine labs (CBC, metabolic panel)

- Symptom flare: think inadvertent gluten ingestion, microscopic colitis, less likely malignancy

---

**Celiac Disease Dilemmas**

- Self-imposed gluten free diet - confounds diagnostic testing (except HLA type)

- The patient who will not eat gluten
  - OK if nutritionally sound

- "Diagnosis" on basis of single positive test (e.g. gliadin antibodies, HLA type)

- Gluten "sensitivity"
### Summary Points

- Test before treating

- You won't find what you don't look for: associated conditions and endoscopic findings

- Use the best serology strategy (Ig A anti-tTG Ab) if not Ig A deficient

### Summary Points

- Recognize risk groups and remember iron deficient anemia

- Diet "cures" the manifestations of the disease

- Follow the patient