Discordant Celiac Serology and Biopsies: What to do?

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Boston Children's Hospital
Until every child is well

CELIAC RESEARCH PROGRAM
HARVARD MEDICAL SCHOOL

Disclosures

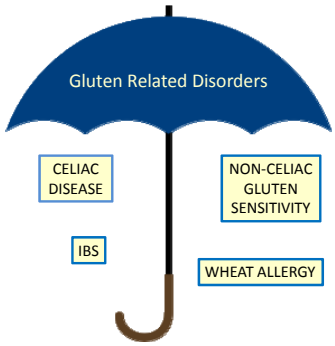
In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

Celiac Disease

- Chronic small intestinal immune-mediated enteropathy
- Precipitated by exposure to dietary gluten (from wheat, rye and barley)
- Genetically predisposed individuals (HLA DQ2/DQ8)
- Wide range of clinical presentation in children
- Affects approximately 1%
- Treatment with a 100% strict gluten free diet

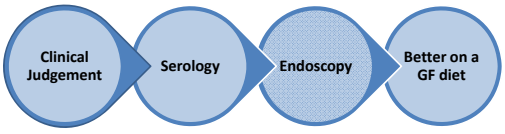
Oslo Definitions for coeliac disease and related terms. Gut 2013.

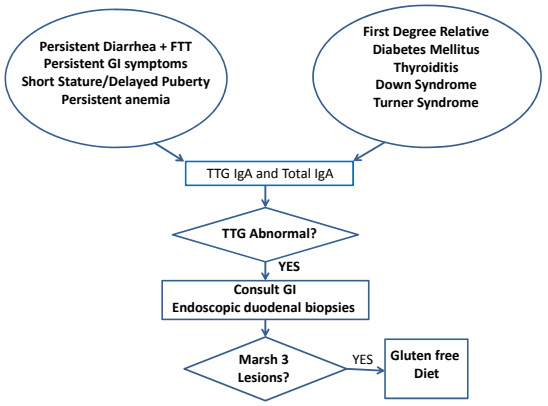
Gluten Free Explosion



Evaluate for celiac disease before going gluten free

Celiac Disease: Making the Diagnosis





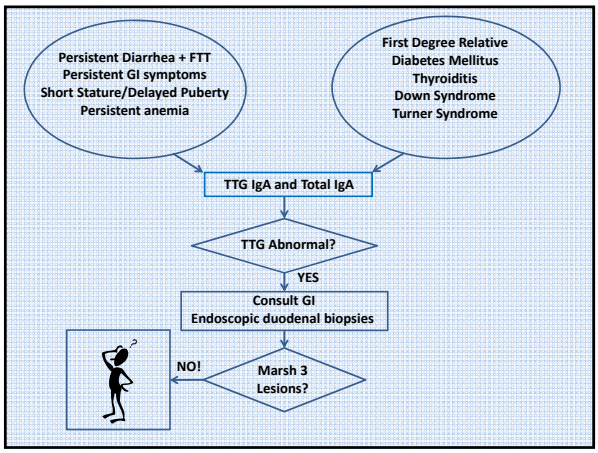
Discordance: Serology and Biopsy

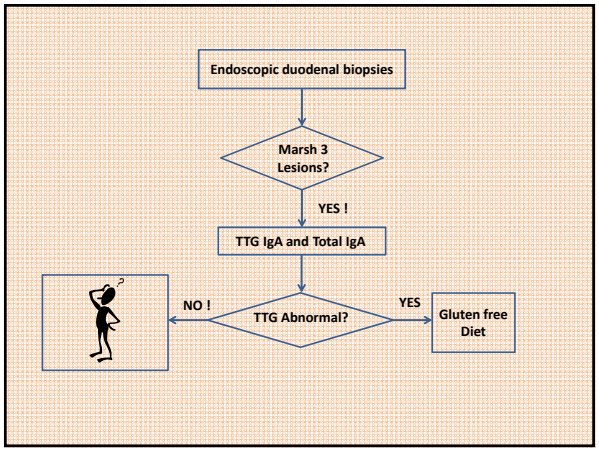
Endoscopy images thanks to Victor Fox

Learning Objectives

Upon completion of this session, the learner will be able to:

1. Recognize potential complexities in the use of celiac serology and small intestinal biopsies when evaluating for celiac disease
2. Apply a clinical approach to evaluate and treat children with discordant celiac serology and small bowel biopsies





Discordance: An Approach

1. #1. Reassess your patient
2. #2. Reassess your serology
3. #3. Reassess your biopsies
4. #4. Consider HLA typing (DQ2/DQ8)
5. #5. Consider more evaluation
6. #6. Develop a thoughtful treatment/monitoring plan

Case A: TTG +/Biopsy -

5 year old girl with intermittent abdominal pain and episodes of arthralgia.

- TTG IgA: 43 (normal < 19)
- Duodenal biopsies: normal (Marsh 0)

Case A: #1 Your patient

Assess your patient's gluten intake

- Had they recently been gluten free?
- If yes, when and for how long?
- Were they consuming gluten at the time of the endoscopy?
- How much gluten were they getting?
- How long had they been getting gluten?

Case A : #1 Your patient

Gluten challenge data in children show variability in the time of onset of:

- Symptoms
- Positive serology
- Mucosal relapse

Children with suspected or diagnosed CD on a gluten challenge

- Almost all developed increased IELS counts within 1 month
- 51-100% developed mucosal relapse in 2-3 months

Bruins, M. The Clinical Response to Gluten Challenge: A Review of the Literature. Nutrients 2013.

Case A : #1 Your patient

Reassess signs and symptoms

- What are the signs or symptoms? How severe?
- Are there other potential causes that can be treated?
- Do the signs or symptoms point towards other potential causes for a false positive TTG IgA?
- Is there a condition that predisposes them to false positive TTG IgA levels?
- Are they asymptomatic?

Are they high risk?

- Family member with celiac, T1DM, thyroiditis, Downs syndrome

Case A : #2 The Serology

Can you trust your positive TTG IgA?

Excellent test performance at the time of diagnosis

Sensitivity:	>95%
Specificity:	>97%

Is it as good as we think?

Giersiepen et al. Accuracy of Diagnostic Antibody Tests for Celiac Disease in Children. Gastroenterology 2012.

Case A : #2 The Serology

Limitations of TTG IgA

- Fluctuating levels in individuals over time
- Variation in performance characteristics of different assays
- False positive TTG IgA levels seen
  - IBD
  - Connective tissue disease
  - Type 1 Diabetes Mellitus (T1DM)

Aurricchio et al. Potential Celiac Children: 9- year Follow-up on a Gluten containing Diet. American Journal of Gastroenterology 2014.
Li et al. A Report on the International Transglutaminase Autoantibody Workshop for Celiac Disease. American Journal of Gastroenterology 2009.
Bizzaro et al. IgA and IgG Tissue Transglutaminase Antibody Prevalence and Clinical Significance in CTD, IBD and PBC. Digestive Diseases and Sciences 2003.
Franzese et al. Potential celiac disease in type 1 diabetes: A multicenter study. Diabetes Research and Clinical Practice 2011.

Case A : #2 The Serology

Limitations of TTG IgA:

- Variability in "real-life" test performance in commercial/clinical laboratories
  - Adults: 102/122 diagnosed with CD with TTG IgA
    - Pooled Sensitivity: 70.6%
    - Pooled Specificity: 65%
  - 89% samples tested at 1 of 2 laboratories
    - Sensitivity: 40-86%
    - Specificity: 41.7-100%
- Similar evidence of diminished "real-life" test performance in pediatrics

Abrams et al. Utility in Clinical Practice of Immunoglobulin A Anti-Tissue Transglutaminase Antibody for the Diagosis of Celiac Disease. Clinical Gastroenterology and Hepatology 2006.
Weir et al. Manuscript in progress.

Case A : #2 The Serology

- Repeat TTG IgA
- Consider additional serologic markers

	Sensitivity	Specificity
Endomysial IgA (EMA IgA)	>90	98%
Deamidated gliadin IgG (DGP IgG)	80- 99%	86-97%

Giersiepen et al. Accuracy of Diagnostic Antibody Tests for Celiac Disease in Children. Gastroenterology 2012.

Case A : #3 Biopsies

Assess the quality of your biopsies

- Processing and orientation
- Adequate size and sampling

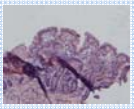
Reassess for histopathology

- Are IELs present?
- Are their other findings that can explain your patients symptoms/serologic findings?
  - Eosinophilic esophagitis, granulomas

Case A : #3 Biopsies

In confirmed pediatric CD cases:

- Over 50% had variation of at least one Marsh grade between separate fragments in a biopsy set
- 36% demonstrated at least one normal biopsy
- 10% had findings only in the bulb



Bulb only disease and patchiness necessitates adequate sampling.

2 bulb biopsies
4 duodenal biopsies

Weir et al. Variability of Histopathologic Changes in Childhood Celiac Disease. American Journal of Gastroenterology 2010.

Case A : #3 Biopsies

Prevalence of intestinal TTG IgA deposits:

- Children with untreated CD: 73-100%
- Children with positive serology/no villous atrophy:
- 68-100%
- TTG IgA intestinal deposits may precede the development of mucosal damage in celiac disease
- Pediatric controls: 5-20% (increased in T1DM and IBD)

Gatti et al. Beyond the intestinal celiac mucosa: diagnostic role of anti-TG2 deposits, as systemic review. Frontiers in Medicine 2014.

Case A : #4 Genetics

HLA typing for DQ2 and DQ8

- "Necessary, but not sufficient"
- 95% of patients HLA-DQ2, most of the remainder are HLA-DQ8
- 30% of the population carry DQ2

Main role of HLA typing to exclude the diagnosis of celiac disease

If negative, very low likelihood of ever developing celiac disease

Kupfer et al. Celiac Disease Pathophysiology. Gastrointestinal Endoscopy Clinics of North America 2012.

Case A : #4 Genetics

Identification of "High-risk" children

Prospective infant feeding studies

- First degree family member with celiac disease
- DQ2 homozygous
- Developed CD more frequently and earlier
  - **26-27% by 5 years of age**

TEDDY Study:

- Estimated cumulative risk of CD autoimmunity by 5 years = 26%

Lionetti et al. Introduction of Gluten, HLA Status and the Risk of Celiac Disease in Children. NEJM 2014.
Vriezinga et al. Randomized Feeding Intervention in Infants at High Risk for Celiac Disease. NEJM 2014.
Liu et al. Risk of Pediatric Celiac Disease According to HLA Haplotype and Country. NEJM. 2014.

Case A: #5 Additional Evaluation

Strong correlation between distal duodenal (2nd or 3rd part) and jejunal mucosal specimens

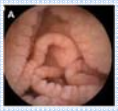
Jejunal only disease is rare but has been reported

Enteroscopy

- New cases revealed with previous negative duodenal histology
- Invasiveness and availability limits use

Video Capsule Endoscopy

- Pooled sensitivity at diagnosis: 89%
- Pooled specificity at diagnosis: 95%
- Use in followup of serology +/duodenal biopsy - cases
- Risk and availability issues limits use



Meijer et al. Small intestinal biopsies in celiac disease: duodenal or jejunal? Virchows Arch 2003
Boayraktar et al. Is enteroscopy necessary for diagnosis of celiac disease. WJG 2012.
Tennyson et al. Video Capsule Endoscopy in Celiac Disease. Gastrointest Endo Clin N Am 2012.

Case A: #5 Additional Evaluation

If other conditions suspected:

- Other blood work (ESR, CRP, albumin, CBC, etc)
- Small bowel imaging (MRI enterography, UGISBFT)
- Colonoscopy

Case A : TTG IgA + / biopsy -

Potential Celiac Disease

- Positive CD serology
- Normal small intestinal mucosal architecture
- HLA DQ2 or DQ8

Treatment plan: Gluten free or not?

Oslo Definitions for coeliac disease and related terms. Gut 2013.

Potential CD in children

175/210 children with potential celiac disease were asymptomatic and kept on a gluten-containing diet

- Serial serology (every 6 months)
- Repeat small bowel biopsies (every 2 years)
- Up to 9 years (at least 5 years)

Retention rate of 63%

33 % developed CD

Serologic course:	Histologic course:
43% persistently elevated	At 3 years: 86% remained potential
20% became negative	At 6 years: 73% remained potential
37% with fluctuant levels	At 9 years: 67% remained potential

Aurricchio et al. Potential Celiac Children: 9- year Follow-up on a Gluten containing Diet. American Journal of Gastroenterology 2014.

Potential CD in children

17/59 EMA IgA positive children with normal villous structure

- Majority symptomatic with GI/malabsorption
- 7/8 maintained on a gluten-containing diet developed Marsh 3 lesions within 2 years
- 12/12 who ended up gluten free showed improvement in both symptoms and serology
- 1 patient had rising antibodies/flatulence, increased IELs only (Marsh 1) and stayed on gluten

Kurppa et al. Celiac Disease without Villous Atrophy in Children: A Prospective Study. Journal of Pediatrics 2010.

Case B: TTG - / Biopsy +

14 year old with persistent reflux and heartburn.

- Villous atrophy found in duodenal biopsies
- TTG IgA: 4 (normal <19)

Case B: #1 Your patient

Assess your patient's gluten intake
- Did they restrict their gluten intake before the serology was sent?
- If yes, when and for how long?

Reassess their signs and symptoms
- How severe are their symptoms?
- Do the signs or symptoms point towards other diagnoses that cause villous atrophy?

Are they high risk?
- Family member with celiac, T1DM, thyroiditis, Downs syndrome

Case B: #2 The Serology

Can you trust your negative TTG IgA?

Total IgA status:
- Selective IgA deficiency has increased prevalence in patients with CD (2%)
- Low IgA levels can lead to false negative serology

Cataldo, F et al. Celiac disease and selective immunoglobulin A deficiency. Journal of Pediatrics 1997.
Chow et al. Immunoglobulin IgA Deficiency in Celiac Disease. Journal of Clinical Gastroenterology 2012.

Case B: #2 The Serology

Limitations of TTG IgA:

- Fluctuating levels in individuals over time
- Variation in performance characteristics of different assays
- Variability in "real-life" test performance in commercial/clinical laboratories

Case B: #2 The Serology

Variability in "real-life" test performance in pediatrics

- 179 Children with suspected CD, obtained TTG IgA at endoscopy
  - Sensitivity TTG IgA 79%
  - 10/78 patients with M3 lesions were seronegative
    - 7/10 had positive TTG IgA prior to the endoscopy
    - 1/10 had low IgA/positive TTG IgG
    - 2/10 started GFD with improvement

Weir et al , manuscript in preparation

Case B : #2 The Serology

- Repeat TTG IgA
- Consider additional serologic markers

	Sensitivity	Specificity
Endomysial IgA (EMA IgA)	>90	98%
Deamidated gliadin IgG (DGP IgG)	80- 99%	86-97%

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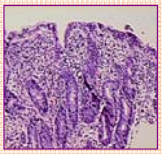
Case B: #3 Biopsies



"All that flattens is not celiac"

- IBD
- Autoimmune enteropathy
- CVID
- Infection (giardia, viral)
- Medication-related
  - (NSAIDs, chemotherapy, mycophenolate mofetil, azathioprine)
- Non-gluten protein intolerance
- Bacterial overgrowth

Review with your pathologist

- Presence of IELs?
- Presence of neutrophil-rich inflammation/crypt abcesses/granulomata?
- Presence of apoptosis? Absence of goblet or Paneth cells?
- Expansion of plasma cell in the lamina propria or paucity of plasma cells?
- TTG IgA deposits present?

Pai, RK. A practical approach to small bowel biopsy interpretation: Celiac disease and its mimics. Seminars in Diagnostic Pathology 2014.

Case B: #4 Genetics

HLA typing for DQ2 and DQ8

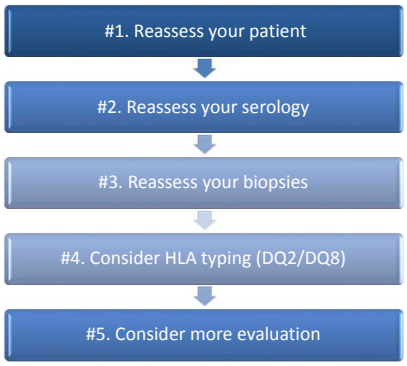
- "Necessary, but not sufficient"
- 95% of patients HLA-DQ2, most of the remainder are HLA-DQ8
- 30% of the population carry DQ2
- If negative, very low likelihood of ever developing celiac disease
- DQ2 homozygous may confer significantly higher-risk in some children

Kupfer et al. Celiac Disease Pathophysiology. Gastrointestinal Endoscopy Clinics of North America 2012.

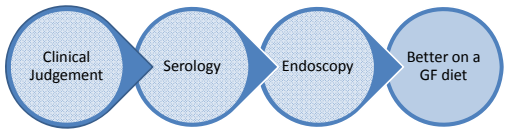
Case B: #5 Additional Evaluation

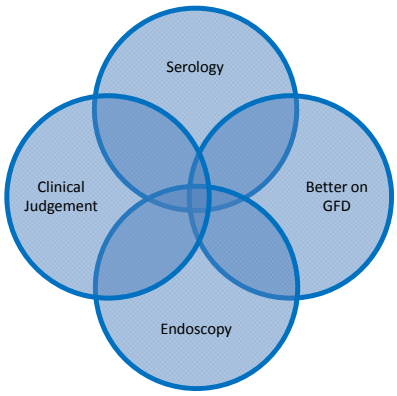
- Bloodwork:
  - Inflammatory markers?
  - Anti-enterocyte antibodies? IPEX or CTLA-4?
  - Immunologic workup?
- Stool studies (lactoferrin, giardia)?
- Small bowel imaging (MRI enterography, UGISBFT)?
- Colonoscopy?

Discordance: An Approach



Celiac Disease: Making the Diagnosis





Discordance: An Approach

#6. Develop a thoughtful treatment/monitoring plan

VS

Gluten Free Diet

Upsides vs Downsides

Symptom relief	Difficult to do correctly
Growth Optimization	Requires education of family by knowledgeable dietician
Maximization of bone mineralization	Suboptimal adherence has risk
Reduction of long-term celiac associated morbidities	Risk of increased BMI
Relief of provider angst	Risk of inadequate nutrition
	High economic burden
	Negative QOL implications

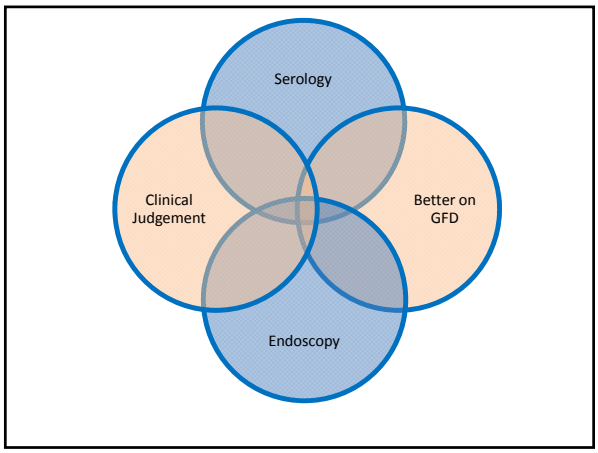
Treatment without a clear diagnosis

Know where you are starting from

Decide on a treatment plan:
Gluten-*free* vs Gluten-*full* trial

If gluten-free trial,
provide complete support and educational resources

Monitor with repeat clinical, serologic and histopathologic evaluation


Serology
Clinical Judgement
Better on GFD
Endoscopy