Celiac Disease and Non Celiac Gluten Sensitivity

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DISCLOSURE

Commercial Interest
None

Off Label Usage
None
Learning Objectives

• Review the clinical presentation of celiac disease

• Discuss non celiac gluten sensitivity and distinguish from celiac disease
Celiac Disease
Definition

Chronic autoimmune disease with a characteristic small bowel lesion which impairs absorption and responds to gluten withdrawal
Non Celiac Gluten Sensitivity

Definition

A clinical entity induced by the ingestion of gluten leading to intestinal and/or extraintestinal symptoms that resolve once gluten-containing food products are eliminated from the diet. Celiac disease and wheat allergy must be ruled out first.

Fasano et al
GE 2015
Wheat allergy

• 0.1% of population with true wheat allergy
• IgE mediated reaction to gliaden
• No reason to restrict barley, rye, or oats
• Systemic allergic reaction
• Typically self-limited by age 5

Pietzak, M
JPEN 1/12
Prevalence of Celiac Disease

- 1980 = 1:500 - 1:8000 (general population)
- 2007 = 1:100 - 1:200
- Increasing frequency in African Americans, Middle East, and Asia
- Only 10-15% with CD are diagnosed
- Prevalence increased 4-5 fold over past 30 yr

Crowe, Sheila
Annals IM, 5/2011
Etiology / Pathogenesis

- Genetic basis (HLA DQ2, DQ8)
- Immune mediated: Innate/Acquired
- Environmental factors - tolerate 10-50 mg gluten daily (bread = 1.6 gr/slice)

Fasano and Catassi
NEJM, 2012
Etiology / Pathogenesis

- High proline / glutamine content play key role in pathogenesis
- Relatively resistant to proteolytic enzymes
- Enhanced binding of peptides to DQ2/8
- Peptide - DQ complex activates T cells
Etiology / Pathogenesis

• Earliest changes <1 hour after exposure to gluten

• Increased intraepithelial lymphocytes (function unclear)

• Up-regulated IL-15 expression by enterocytes

• Activates lymphocytes $\Rightarrow$ NKC
Serological Tests

• Deamidated anti-gliaden Ab (IgA & IgG)
• Anti-endomysial Ab
• Anti-tissue transglutaminase
Diagnostic Testing for Celiac Disease

- Prevalence of CD ranged from 2 – 13%
- Diarrhea: sens = 27- 86%, spec = 21- 86%
- Overall abd sx’s were poor predictors of CD
- IgA-TTG and EMA are most accurate

Van der Windt et al
JAMA 5/2010
Anti-Tissue Transglutaminase

- Major endomysial autoantigen
- Released during wounding
- ELISA assay
- Highly sensitive / specific
Anti-Tissue Transglutaminase

- Cross-links proteins
- Glutamine deamidated to glutamic acid (negatively charged)
- Enhanced binding to disease associated DQ2 or DQ8
- Activate DQ2 or DQ8 restricted T cells
Pitfalls in Diagnosis in Celiac Disease

- Selective IgA deficiency in 2-5%
- Titers reflect degree of villous atrophy
- False (+) with liver disease, DM
- Proximal involvement may be patchy - need multiple biopsies
- Poor orientation of biopsy may miss disease
NCGS: Clinical Picture

- Median age: 40, M:F = 1:2.5
- IBS: pain, bloating, altered bowel habits
- Systemic features: HA, mental “fog”, joint and muscle pain, parasthesia, depression, skin rash
- No associated autoimmune comorbidities
- No evidence to suggest NCGS is permanent: Consider rechallenge after 1-2 years

Volta and DeGiorgio
Nat Rev Gastro and Hep, 2012
Non Celiac Gluten Sensitivity: Pathogenesis

- Increase in expression of innate immunity marker Toll-like receptors, IFN-γ
- No increase in adaptive receptors, e.g. IL-6, TNF-α, IL-17 and IL-21
- Increase in intestinal permeability (?)
- Increased intraepithelial lymphocytes
- Confocal endomicroscopy: 2/3 with break in TJ

Volta and DeGiorgio
Nat Rev in Gastro and Hep, 2012
Fasano et al, GE 2015
Non Celiac Gluten Sensitivity: Pathogenesis

• May not be entirely mediated through gluten
• ATI’s: plant derived proteins that inhibit enzymes of common parasites
• ATI’s: may be the inducer of innate immunity in NCGS

Fasano et al
GE, 2015
Mucosal Cytokine Release in NGCS

- Reverse transcriptase PCR in mRNA for several cytokines and chemokine
- Gene array examination
- Results: CD (11 patients), NCGS (22 patients) given gluten challenge
- CD: Increased IL8, TNFα
- NCGS: increased INFγ plus mRNA - INFγ

Brottveit et al
AJG, 5/13
Symptoms reported by 78 patients with gluten sensitivity; most patients complained of two or more symptoms.

Volta and DeGiorgio: Nat Rev Gastro and Hep, 2012
Non Celiac Gluten Sensitivity

• 2015: 25% USA on GFD, $11.6B industry
• 25-50% IgG AG Antibodies
• HLA DQ2/8 in 24-100%
• Increased IEL’s c/w Marsh 1
• True prevalence: 0.7 – 7.0%

Bardella et al
Curr Gastro Rep 2016
Non Celiac Gluten Sensitivity

- Gluten may not be the sole component of wheat responsible for the symptoms
- Unabsorbed carbs may contribute
- Gluten may alter intestinal motility through opiate receptors
- Gluten causes low-grade inflammation in animal models

DiSabatino and Corazza
AIM, 2012
Gluten Intolerance

- DB, R, PC trial of gluten in IBS patients w/o celiac disease
- Patients were randomized to diet with or without gluten for up to 6 weeks
- 34 patients completed trial
- Evaluated: symptoms, markers of inflammation (CRP, fecal lactoferrin, serologies, and intestinal permeability)

Biesiekierski et al
AJG, 3/11
Gluten Intolerance

Results

- Significant increase in pain, lack of satisfaction with BM, and tiredness in gluten group
- Trend only for overall sx’s, wind, and nausea
- No change in any biomarkers of inflammation
- No change in celiac serologies

Biesiekierski et al
AJG, 3/11
NCGS vs FodMAP Diet

• R, DB, PC trial with 3 different diets containing gluten (none, low, high)
• Crossover trial (low FodMAP) between 3 diets
• Patients improved on low FodMAP yet no impact from gluten addition
• FodMAP may play larger role in symptoms

Biesiekierski et al
GE 2013
Gluten Challenge in NCGS

- DB, PC crossover gluten challenge in NCGS
- 59 patients with gluten related symptoms
- Gluten challenge of 4.375 g/day for one week
- Outcome: Change in symptoms
- Results: overall symptom score significantly higher on gluten, yet results driven by only 9 patients

DiSabatino et al
CGH, 9/15
Non Celiac Wheat Sensitivity

- 276 patients with NGWS (206 with other food sensitivities)
- Results: Increase in AGA, duodenal IEL/eosinophils, and colonic eosinophils
- 50% WS alone with AGA, increased HLA DQ2/8, and duodenal IEL (94%)
- No increased markers of inflammation before/after challenge

Carroccio et al
AJG, 12/12
Non Celiac Gluten Sensitivity

• Food intolerance: Body lacks specific enzyme to digest nutrient
• Food sensitivity: Immune mediated reaction to a specific nutrient
• NCGS is a food sensitivity
Non Celiac Gluten Sensitivity

- Not a food intolerance
- A diagnostic challenge may often be beneficial
- Increase small bowel permeability if HLA DQ 2/8 (+)
- Specific biomarker to identify disease is lacking
- IBS: 30% with an NCGS

Vazquez–Roque and Oxentenko
MCP, 9/15
CD versus NCGS

- 238 subjects: 125 w/NCGS, 101w/CD

Approach to diagnosis

Kabbini et al
AJG 5/14
Conclusion:
Incorporate risk factors such as family history, gastrointestinal symptoms, and HLA testing if serologies negative, can avoid need for duodenal biopsy

Kabbani et al
AJG, 5/14
Gluten Sensitivity: Problems with Self-treatment

- Subsequent inability to diagnose or exclude CD
- Consequences of incomplete adherence to GFD in undiscovered CD
- High cost of GFD in a non-celiac patient

DiSabatino and Corazza
AIM, 2012
Downside to GFD

• 25% of Americans consumed gluten free food
• 67% increase 2013–2015
• Rice is major substitute
• Increased urinary arsenic and serum mercury

Bulka et al
Epidemiology, 2017
Pitfalls of gluten-free diet

- 55 patient’s on gluten-free diet >2 years c/w 50 newly diagnosed CD : F/U 12 months

GFD:
1) increased nutrient consumption
2) inadequate intake folate, ribavirin, vitamin C
3) deficiencies in fiber, thiamine, calcium, vitamin A, and iron
4) weight gain ~3 kg and increased sat fat

Shepherd and Gibson
J Human Nutrition and Dietetics, 2012
Nutritional Status

• Increased homocysteine levels
• B6 decreased in 11/30 (37%)
• Folate decreased in 6/30 (20%)
• B12 level normal in all
Conclusions

• Gluten sensitivity is poorly understood and no distinct marker exists
• No clear associated autoimmune comorbidities
• Gluten alone may not be factor in clinical symptoms
• Reasonable to consider trial of GFD, but may reintroduce gluten at later date