CELIAC DISEASE

Charles H. Miranda, MD, FACP

South Denver Internal Medicine

HISTORY

- Dutch pediatrician Willem K Dicke recognized an association between eating breads and cereals and relapsing diarrhea- World War II
- Small biopsy first described-1954
- Tissue transglutaminase antibody-1997

DEFINITIONS

Celiac Disease: A heightened immune response to the gliadin or other prolamine components of gluten in genetically predisposed individuals (HLA) leading to autoimmune intestinal damage often with systemic manifestations. Prevalence 1%.

Refractory Celiac Disease: Celiac disease that does not respond to gluten free diet after two years. Prevalence 5% of celiac patients.

Non-celiac gluten sensitivity: Symptoms related to gluten or other wheat protein exposure. No intestinal damage. ? Innate immune response. Prevalence ? 4-6%.

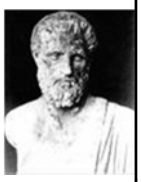
Wheat Allergy: Adverse reactions involving IgE antibodies to one or more proteins found in wheat. This is not an autoimmune response. Prevalence 0.3%

PREVALENCE

- 1:70 to 1:300 (most countries)
- United States Study
- 1:22 (primary relative)
- 1:39 (secondary relative)
- 1:56 (patient with at risk symptoms)
- 1:133 (patient with no risk factors)
- Italian Study: 15% of newly diagnosed celiacs were > 65 years old.
- 1:100-1:250 white Northern European Ancestors.
- Rare in Chinese, Japanese and Africans (sub-Saharan)

HISTORY

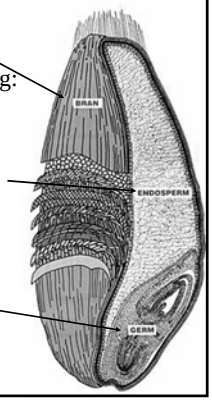
- 50 A.D. - Aretaeus a Greek physician from Cappadocia (Turkey) "If the stomach be irretentive of the food and if it pass through undigested and crude, and nothing ascends into the body, we call such persons koeliacs"



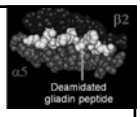
- 1888 - *Samuel Gee* a English physician and pediatrician "On the Coeliac Affection...if the disease is to be cured at all it must be by means of diet"

What is Gluten?

- Bran: outer layer containing:
  - Fiber, B vitamins, Minerals, Protein
- Endosperm: middle layer containing:
  - Gluten: Protein containing nitrogen needed for germination
  - Carbohydrates
- Germ: inner layer containing:
  - Minerals, B Vitamins, Vitamin E

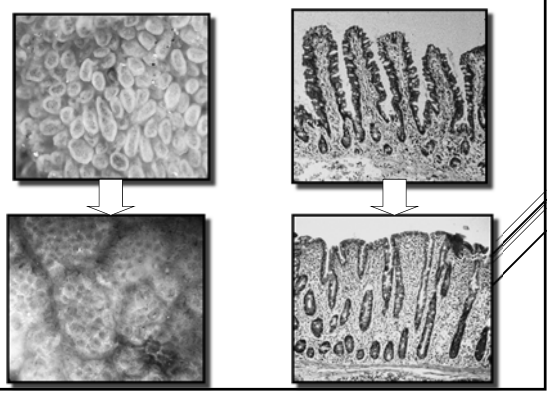


WHAT IS GLIADIN?



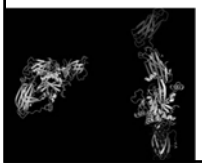
- Gliadin is a peptide (sub-protein) of gluten
- Gliadin receptors on intestinal epithelial cells may mediate the transport of gliadin peptides to the lamina propria where T cell activation occurs.
- The dominant amino acid sequence responsible for T cell response is a deaminated glutamine of alpha gliadin.
- Certain amino acid sequences in gliadin that are rich in proline are particularly resistant to peptidases (protein degrading enzymes) in the intestines. These regions initiate inflammation.
-

Intestinal Damage in Celiac Disease



What is Tissue Transglutaminase (tTG)?

- tTG is an enzyme found in all cells.
- tTG cross links glutamine rich proteins such as gluten
- tTG deamidates glutamine in gluten. This resultant negative charge increases the binding of gluten to HLA DQ2 and DQ8 antigen presenting cells. This results in an increased stimulation of T cells



HISTOLOGY CLASSIFICATION

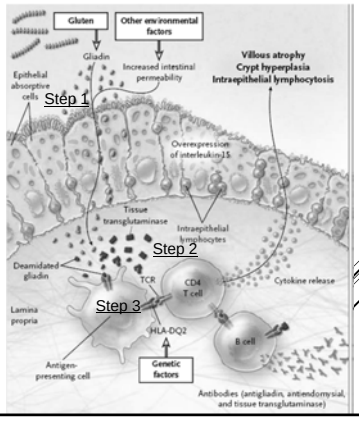
- Marsh Oberhuber Classification
  - Type 0 (normal)
  - Type 1 (intraepithelial lymphocytes only)
  - Type 2 (intraepithelial lymphocytes and crypt hyperplasia)
  - Type 3a (intraepithelial lymphocytes, crypt hyperplasia and partial villous atrophy)
  - Type 3b (intraepithelial lymphocytes, crypt hyperplasia and subtotal villous atrophy)
  - Type 3c (intraepithelial lymphocytes, crypt hyperplasia and total villous atrophy)
  - Find a pathologist who is familiar with celiac disease

PATHOPHYSIOLOGY

Step 1: Gliadin entry into the submucosa

Step 2: Deamidation of gliadin by Tissue Transglutaminase (tTG)

Step 3: Immune Activation: Only HLA DQ2 and DQ8 are able to bind gliadin!



Green, Cellier NEJM 2007

Symptoms

Classic Symptoms	Non-Classic Symptoms
-Diarrhea -Iron deficiency with or without anemia -Abdominal Pain -Weight Loss/Failure to thrive -Fatigue/lethargy -Bloating/gas -Dermatitis herpetiformis	-Asymptomatic -LFT elevations -Constipation -Aphthous ulcers -Nausea/Vomiting -Heartburn/GERD -Hyposplenia -Pancreatitis -Arthralgias/Myalgias -Neuropathy/Ataxia -Alopecia -Headaches/Migraines -Osteopenia/Osteoporosis -Dental defects -Fertility problems -Cognitive impairment/Depression

DIAGNOSIS-ANTIGLIADIN ANTIBODY

- 15-20% false positive rate
- Many normal people have elevated IGA and IGG anti-gliadin antibodies

DIAGNOSIS-DEAMINATED GLIADIN PEPTIDE ANTIBODY

- Uses synthetic gliadin peptides that mimic tTG modified gliadin sequences to capture serum IGA or IGG against deaminated gliadin peptide
- Sensitivity 92-94%
- Specificity 99-100%
- Levels can be used to monitor the effectiveness of treatment.

DIAGNOSIS-IGA ENDOMYSIAL ANTIBODY

- Indirect immunofluorescence
- Target antigen is tTG
- Moderately sensitive
- Highly specific
- Levels can be used to monitor the effectiveness of treatment.

DIAGNOSTIC CHALLENGES

- History and symptoms consistent with celiac disease but tTGA is negative
  - Measure DGPA and HLA Typing
  - Low IGA (measure IgG tTGA and DGPA, HLA typing)
  - Already on a gluten free diet
  - Wheat allergy (IgE to wheat)
  - Non-celiac gluten sensitivity

DIAGNOSIS-TTGA

- Tissue Transglutaminase Antibody-IgA
- ELISA
- Sensitivity 90-98%; Specificity 95-97%.
- False positives are rare especially if the assay uses human tTG.
- Levels can be used to monitor the effectiveness of treatment.

CELIAC VS. GLUTEN SENSITIVITY

- Celiac Disease
  - Symptoms are systemic
  - Gluten
  - Prevalence 1%
  - Genetic inheritance
  - Autoimmune
  - Antibodies identified
  - Abnormal biopsy
  - Improves on a GF diet
- Gluten Sensitivity
  - Symptoms are mainly GI but can be systemic
  - Gluten or other protein
  - Prevalence ? 4-6%
  - No known genetic inheritance
  - ? Innate immune
  - No antibodies
  - Normal biopsy
  - Improves on a gluten or wheat free diet

IMMUNE SYSTEM 101

- Autoimmune response
- Adaptive immune response
  - Long term
  - Custom memory
- Innate immune response
  - Short term
  - No memory

DIAGNOSTIC CHALLENGES

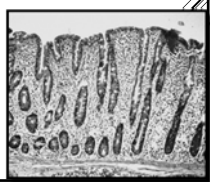
- Patient with symptoms consistent with celiac disease, tTGA is negative, HLA is negative for DQ2 and DQ8, but biopsy shows villous atrophy
  - Other causes of villous atrophy

DIAGNOSTIC CHALLENGES

- History and symptoms are consistent with celiac disease, tTGA is positive yet biopsy is negative
  - False positive tTGA
  - Have pathologist familiar with celiac look at the biopsy
  - Obtain HLA testing
  - Consider gluten challenge and re-biopsy as sampling error from biopsy may have occurred

DIAGNOSTIC CHALLENGE- VILLOUS ATROPHY

- Bacterial Overgrowth
- Crohns
- Casein intolerance
- Eosinophilic gastroenteritis
- Giardiasis
- Lymphoma
- Viral gastroenteritis
- Duodenitis
- Tropical sprue
- ZE syndrome
- CVID
- Autoimmune enteropathy
- AIDS enteropathy
- Low IG sprue
- Olmesartan use
- Whipple disease
- Malnutrition
- TB
- GVH



DIAGNOSTIC CHALLENGES

- Patient has symptoms consistent with celiac disease and she feels better on a gluten free diet. The tTGA is negative and she does not want a biopsy.
  - Obtain HLA typing and if positive suspect celiac disease and continue with gluten free diet.
  - Obtain HLA typing and if negative suspect non-celiac gluten sensitivity and continue on gluten free diet.

CAN I SKIP THE BIOPSY?

- Celiac symptoms
- HLA DQ2 or DQ8
- tTGA > 10 times normal
- EMA positive

CLASSIFICATION OF CELIAC

- Classic Disease
- Atypical
- Asymptomatic (abnormal serology and biopsy)
- Latent (minor or no symptoms, normal biopsy and normal or abnormal serology)

WHAT TESTS SHOULD I HAVE DONE?

- CBC
- Iron studies
- Vitamin B12
- Folate
- Calcium
- Vitamin D
- Parathyroid hormone
- TSH, Free T4
- Complete metabolic panel
- Cholesterol panel
- Vitamins A
- Vitamin E
- Copper
- Zinc
- Carotene
- Thiamine
- Vitamin B6
- Magnesium
- Selenium
- Bone Density
- Celiac antibodies-tTGA and DGPA

WHY DID I DEVELOP THIS NOW?

- Breastfeeding immune benefits
- Time of first exposure to gluten
  - Dr. Catassi's study
    - 800 children
    - Gluten introduction at 4-6 months vs. 12 months
    - Delayed introduction delays onset of disease
  - Sweeden formula 45 with gluten
    - 2 months of age
    - Prevalence increased from 1-8%

ASSOCIATED AUTOIMMUNE DISEASES

- Autoimmune thyroiditis
- Graves Disease
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Rheumatoid arthritis
- Lupus
- Fibromyalgia
- Multiple Sclerosis
- Apthous ulcers
- Dental enamel defects
- Autoimmune neuropathy
- Autoimmune myocarditis or cardiomyopathy
- Diabetes
- Infertility

WHY DID I DEVELOP THIS NOW?

- Role of probiotics or good colonic bacteria
  - Canadian study
    - Vaginal vs. C-section
    - "Good" bacteria passed on during vaginal birth
  - Dr. Fassano's study
    - Children exposed to gluten at 4-6 months vs. 12 months
    - Colonic bacteria of celiac patients is different than normal
    - Strains that help our immune system tolerance against gluten are not represented

WHY DO SOME CELIACS NOT HAVE DIARRHEA?

- Celiac can spare the last portions of the small intestine therefore permitting absorption of nutrients and avoiding malabsorption.
- Causes of diarrhea in celiac disease
  - Inflammation
  - Leaky intestine
  - Bacterial overgrowth
  - Malabsorption

WHY AM I SO TIRED?

- Malabsorption of nutrients
- Iron deficiency
- Chronic inflammation
- Vitamin deficiencies
- Autoimmune diseases-thyroid, adrenal
- Depression

WHY IS THERE AN INCREASED RISK OF CANCER?

- Leaky gut increases systemic exposure to toxins and carcinogens
- Chronic inflammation
- Normal immune surveillance is dysfunctional
- Genetic predisposition

WHY DO CELIAC PATIENTS HAVE OTHER FOOD INTOLERANCES?

- Leaky intestine may allow entry of other immune activating food proteins
- General aberrant immune response to food antigen
- Celiac patients have elevated serum antibody levels of other food proteins
  - Betalactoglobulin (whey protein)
  - Casein (milk protein)
  - Ovalbumin (egg white protein)
  - Avenelin (oat protein)

CANCER RISK

- 2 times more likely overall
- Thyroid cancer 22 times more likely (chronic inflammation)
- Small bowel adenocarcinoma
- Non-Hodgkin's lymphoma 7-9 times more likely and can persists for up to 5 years after GF diet
- Esophageal cancer
- Colorectal cancer
- Hepatocellular carcinoma
- Lung cancer less likely
- Breast cancer less likely

WHY DO I HAVE BONE LOSS?

- Malabsorption of calcium and magnesium
- Vitamin D deficiency
- Secondary parathyroid hormone secretion
- Lack of exercise
- Inflammation affects bone growth
- tTG antibodies affect bone remodeling
- Early menopause

I AM FOLLOWING A STRICT GF DIET BUT I AM STILL NOT FEELING BETTER, WHAT COULD BE WRONG?

- Refractory celiac non-responders after two years of a gluten free diet represents about 5% of celiac patients.
- Inadvertent ingestion of gluten
- Lactose intolerance
- Casein or other food protein intolerance
- Fructose intolerance
- Pancreatic insufficiency
- Microscopic colitis
- Bacterial overgrowth
- Other associated autoimmune diagnosis
- Wrong initial diagnosis (other cause for villous atrophy)
- Lymphoma

IT SAYS THAT IT IS GLUTEN FREE BUT IS IT REALLY?

- The results of the test are only as good as the test itself.
- There are other immune activating amino acid sequences that are not picked up by the test.
- Gluten certified assays
  - R5 ELISA- monoclonal antibody therefore cannot quantify gluten that is broken down (hydrolyzed)
  - R5 ELISA Competitive- Not validated or sensitive but able to quantify hydrolyzed gluten.
  - Morinaga wheat protein ELISA- polyclonal antibody to wheat gliadin. Underestimates barley protein
  - Omega-gliadin ELISA- monoclonal antibody therefore cannot quantify gluten that is hydrolyzed and underestimates barley protein

NEW ADJUNCTIVE TREATMENTS

- Enzyme that breaks down gliadin and gluten
- Suppress the immune response
- Block tTG-bad idea as tTG is present throughout the body and supports wound healing and bone growth
- Prevent gliadin from getting in
  - Gliadin Intestinal Receptor Blockers
  - Zonulin (pre-haptoglobin 2) blockers
  - Drugs that restore the "tight junction"

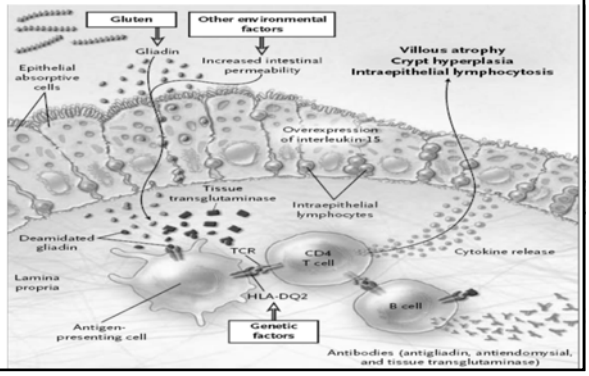
CELIAC IN KIDS VS. ADULTS

- Kids present with more classic symptoms
- Kids present with more malabsorption
- Kids respond to a more diverse set of gliadin and glutenin peptides
- With advancing age the immune response narrows to a few deaminated peptides

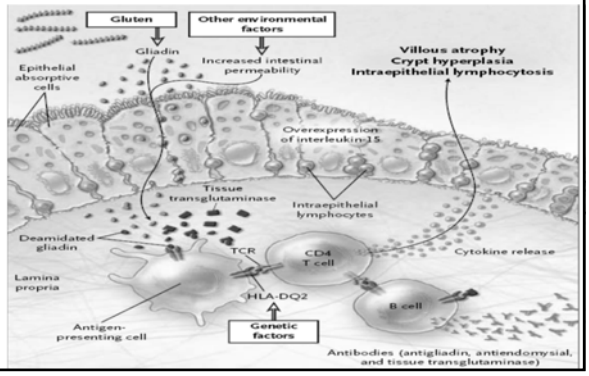
NEW ADJUNCTIVE TREATMENTS IMMUNE MODULATING THERAPY

- Why don't we use drugs in celiac that are known to have benefit in other autoimmune diseases?
- The side effects of immunosuppression limit the use of these drugs in celiac disease

NEW ADJUNCTIVE TREATMENTS



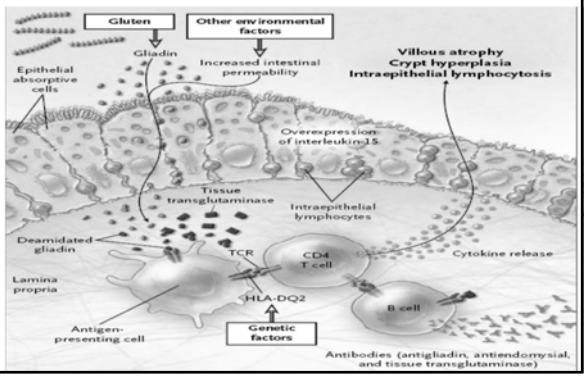
NEW ADJUNCTIVE TREATMENTS



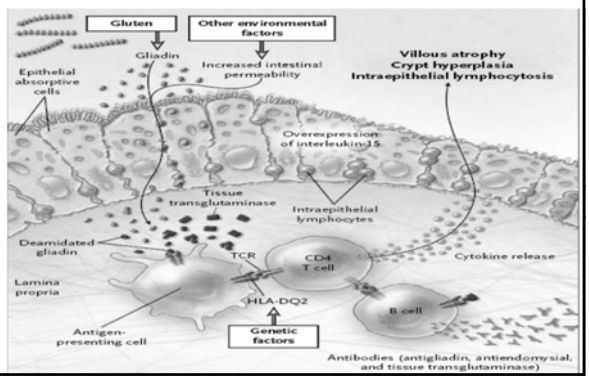
NEW ADJUNCTIVE TREATMENTS- ALV-003

- Combination of two enzymes (proteases) that degrades the "toxic" amino acid sequences (glutamine and proline rich) in gluten thereby reducing the number of immune stimulating proteins
- Must work rapidly and completely
- Alvine Pharmaceuticals
- CeliAction Study-
  - Phase 2b randomized clinical trial
  - Symptomatic patients on a GF diet
  - Endpoint-small bowel biopsy, serology and symptoms

NEW ADJUNCTIVE TREATMENTS



NEW ADJUNCTIVE TREATMENTS



NEW ADJUNCTIVE TREATMENTS NEXVAX 2

- Desensitizing vaccine
- Takes advantage of tolerance or anergy of the immune system (allergy shots)
- Expose the body on a continual basis to the immune activating proteins in gluten without causing anything bad to happen. The immune system will learn tolerance or at least suppress its usual response to the proteins.
- The potential benefit is that of desensitization to a broad array of related amino acid sequences in gluten.
- Immusan T
- Phase 1b safety and tolerability US study for HLA DQ2 patients who are controlled on GF diet.

NEW ADJUNCTIVE TREATMENTS LARAZOTIDE ACETATE

- Regulator of tight junctions
- Tight junctions are the connections between the intestinal epithelial cells
- Zonulin opens the tight junctions
- Larazotide acetate is a protein that prevents the effect of zonulin and tightening up the tight junctions.
- Must be taken shortly prior to any potential exposure to gluten.
- Aliment Pharmacol Ther. 2013;37(2):252-262.