

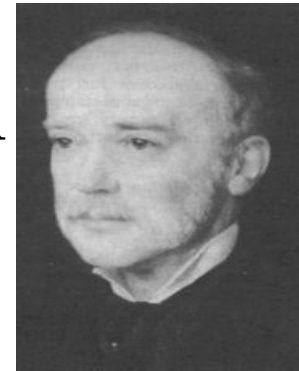


CELIAC DISEASE: IT'S AUTOIMMUNE NOT AN ALLERGY!

**Analissa Drummond PA-C
Department of Pediatrics
Division of Pediatric Gastroenterology**

HISTORY OF CELIAC DISEASE

- Also called gluten-sensitive enteropathy and nontropical spue
- First described by Dr. Samuel Gee in a 1888 report entitled “On the Coeliac Affection”
Term “coeliac” derived from Greek word *koiliakaos*-abdominal
- Similar description of a chronic, malabsorptive disorder by Aretaeus from Cappadochia (now Turkey) reaches as far back as the second century AD



HISTORY CONTINUED

- The cause of celiac disease was unexplained until 1950 when the Dutch pediatrician Willem K Dicke recognized an association between the consumption of bread, cereals and relapsing diarrhea.
- This observation was corroborated when, during periods of food shortage in the Second World War, the symptoms of patients improved once bread was replaced by unconventional, non cereal containing foods.
- This finding confirmed the usefulness of earlier empirical diets that used pure fruit, potatoes, banana, milk, or meat.



HISTORY CONTINUED

- After the war bread was reintroduced. Dicke and Van de Kamer began controlled experiments by exposing children with celiac disease to defined diets. They then determined fecal weight and fecal fat as a measure of malabsorption.
- They found that wheat, rye, barley and to a lesser degree oats, triggered malabsorption, which could be reversed after exclusion of the “toxic” cereals from the diet.
- Shortly after, the toxic agents were found to be present in gluten, the alcohol-soluble fraction of wheat protein.



PATHOPHYSIOLOGY

- Celiac disease is a multifactorial, autoimmune disorder that occurs in genetically susceptible individuals.
- Trigger is an environmental agent-gliadin component of gluten. The enzyme tissue transglutaminase (tTG) has been discovered to be the autoantigen against which the abnormal immune response is directed.
- What is gliadin? A glycoprotein present in wheat and other grains such as rye, barley and to some degree, oats.
- What is gluten? A composite of the proteins gliadin and glutenin which comprise about 80% of the protein contained in wheat seed.



- The pathogenesis of the celiac lesion is thought to be an abnormal permeability allowing the entry of gliadin peptides not entirely degraded by the intraluminal and brush-border bound peptides.
- The most toxic amongst the many fractions of gliadin that have shown to cause the most mucosal damage are very resistant to digestion by gastric, pancreatic, and mucosa-associated enzymes.
- Normally, intestinal epithelium acts as a barrier to the passage of these macromolecules; however in CD there is well documented loosening of the tight junctions which then leads to increased permeability to macromolecules.



- Because of the increased permeability of the macromolecules there are two pathways involved in the pathogenesis.
- The early pathway involves the innate immune system and the subsequent pathway involves the T cells.
- When the toxic gliadin peptides reach the serosal side of the intestinal epithelium an early response by the innate immune system causes crucial modifications of the mucosal microenvironment. The stage is then set for the subsequent involvement of the pathogenic T cells and an inflammatory response.



- 1st phase of T cell involvement reveals a marked increase of HLA-DR (human leukocyte antigen) expression on both the epithelium and the adjacent lamina propria macrophages → overexpression of the intercellular adhesion molecule 1 (ICAM-1) → CD8+ Tcells invade epithelial cells (intraepithelial lymphocytes).
- There are three distinct patterns of mucosal changes that can be recognized:
 - Type 1 infiltrative lesion. Seen in latent phase characterized by morphologically normal mucosa. GI symptoms are usually absent. Intraepithelial lymphocytes are increased followed by infiltration of the lamina propria with plasma and lymphocytes.



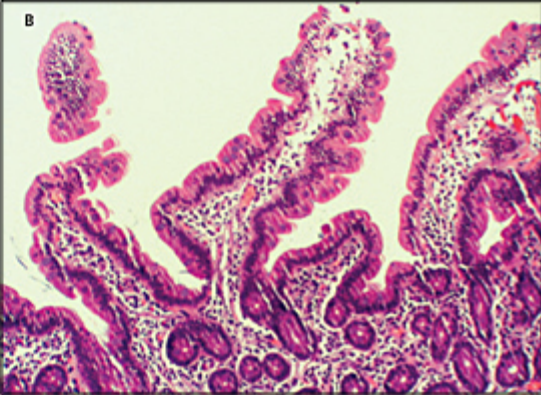
- Type 2 hyperplastic lesion is similar to type 1, but with elongation of crypts due to an increase in undifferentiated crypt cells.
- Type 3 destructive lesion is the most advanced pathologic change. Synonymous with total or subtotal villous atrophy, i.e., the classical lesion originally considered the landmark of CD.



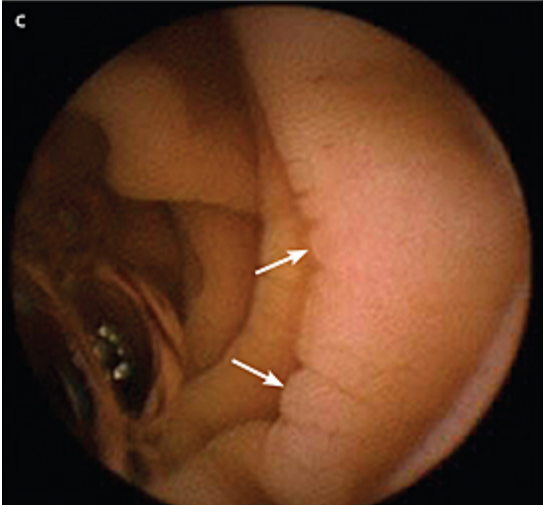
Normal small intestine



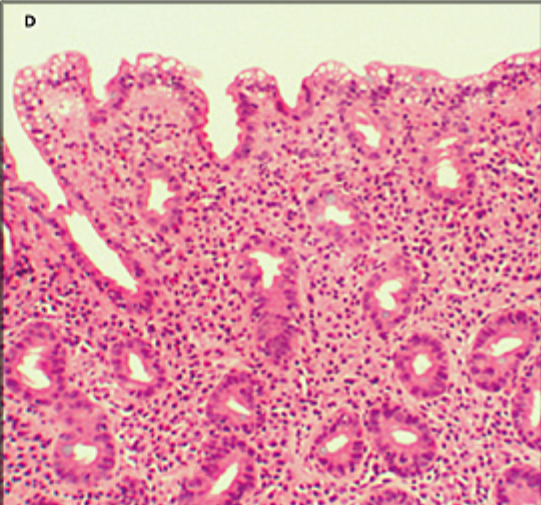
Normal villi



Small intestine with scalloping

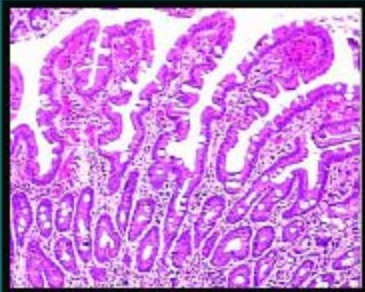


Small intestine with villous atrophy

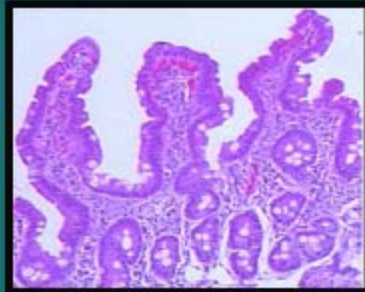


HISTOLOGY OF INTESTINAL BIOPSY IN CD

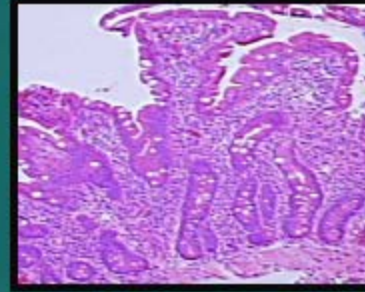
MODIFIED MARSH SCORE



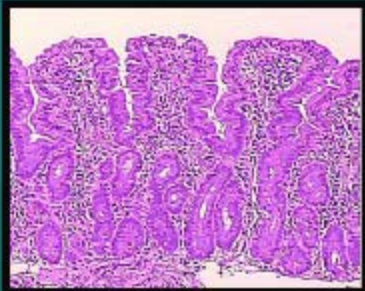
Normal 0



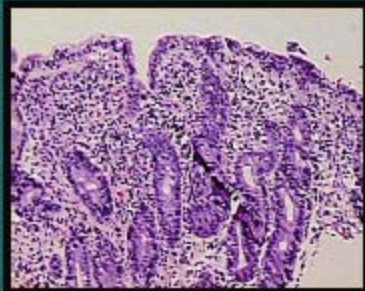
Infiltrative 1



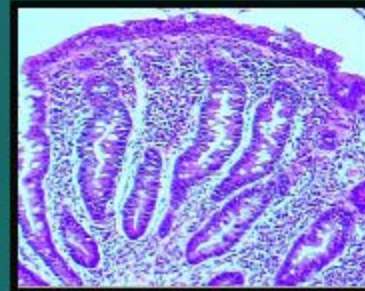
Hyperplastic 2



Partial atrophy 3a



Subtotal atrophy 3b



Total atrophy 3c



- The “Celiac Genes”: HLA DQ2 and DQ8
- Genetic predisposition
 - Human leukocyte antigen (HLA) alleles DQA1 / DQB1 genes encoding DQ2 and / or DQ8 molecules
 - Found in 95% of people with CD
 - 70% concordance in identical twins
- Gene test has 100% predictive value to verify when an individual does not have celiac disease.
- Thirty five percent of anglos have same haplotype, therefore not used to diagnose celiac disease.



EPIDEMIOLOGY

- May be most common predetermined condition in humans
 - Found throughout world
 - Perceived greater incidence in Europe, ↑ gluten in diet
 - Recent screenings found 0.5% to 1% in general population (NIH, 2004; Dube, et al, 2005)
 - 1/77 Swedish children (Carlsson, et al, 2001)
 - 1/230 Italian children (Catassi, et al, 1996)
 - 1/100 5 year old children in Denver (Hoffenberg, et al, 2003)
 - Ethnic distribution unknown
 - Only 3% with CD are diagnosed



- Higher in certain groups (Dube, et al 2005)
 - First degree relative of person with celiac (5-22%)
 - People with type 1 diabetes (3-6%)
 - People with Downs syndrome (5-12%)
 - People with symptomatic iron def. anemia (10-15%)
 - People with osteoporosis (1-3%)
 - ↑'d in Turners and Williams syndrome, selective IgA deficiency, & autoimmune disorders (thyroiditis, hepatitis, Addison)
 - Dermatitis herpetiformis (high correlation)
 - Most with DH have celiac
 - Most with celiac do not have DH



MORTALITY/MORBIDITY

- Morbidity rate can be high.
- Complications range from osteopenia, osteoporosis, or both.
- Infertility in women.
- Short stature, delayed puberty.
- Anemia
- Malignancies (mostly related to the GI tract [eg, intestinal T-cell lymphoma]).
- Overall mortality in patients with untreated celiac disease is increased.



MORTALITY/MORBIDITY

- Evidence also suggests that the risk of mortality is increased in proportion to the diagnostic delay and clearly depends on the diet.
- Subjects who do not follow a gluten-free diet have an increased risk of mortality, as high as 6 times that of the general population.
- Increased death rates are most commonly due to intestinal malignancies that occur within 3 years of diagnosis.
- Some indirect epidemiological evidence suggests that intestinal malignancies can be a cause of death in patients with undiagnosed celiac disease.



AGE/RACE/SEX

- Celiac disease can occur at any stage in life; a diagnosis is not unusual in people older than 60 years.
- In some ethnicities, such as in the Saharawi population, celiac disease has been found in as many as 5% of the population. Celiac disease is considered extremely rare or nonexistent in people of African, Chinese, or Japanese descent.
- Most studies indicate a prevalence for the female sex, ranging from 1.5:1 to 3:1.



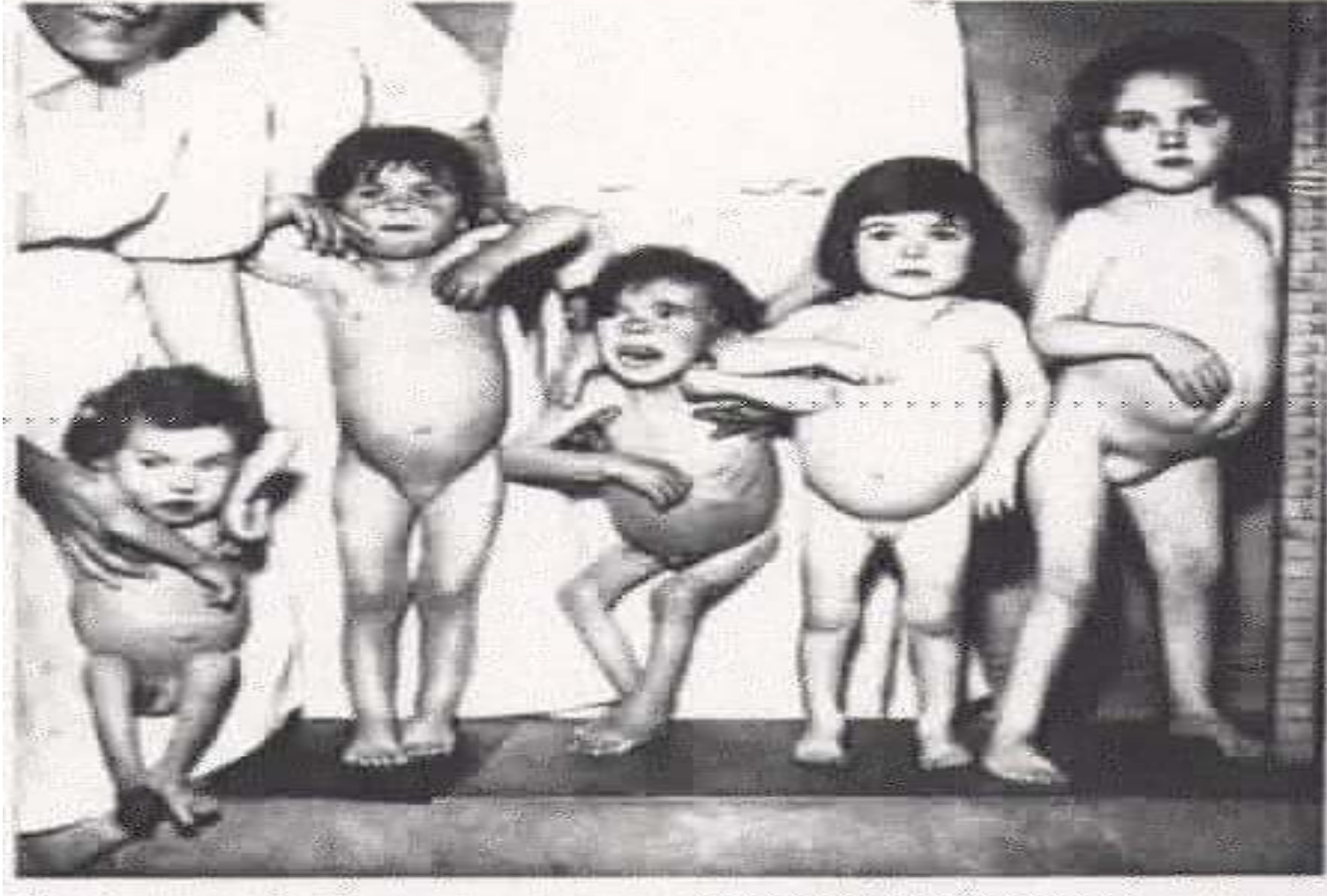
CLINICAL SYMPTOMS OF CELIAC DISEASE

- Classic celiac disease
 - Abdominal pain
 - Diarrhea, constipation
 - Gassiness, distention, bloating
 - Anorexia
 - Poor weight gain, FTT (but can be obese)
 - Irritability, lethargy

(NIH, 2004)



CLASSIC PHYSICAL PRESENTATION

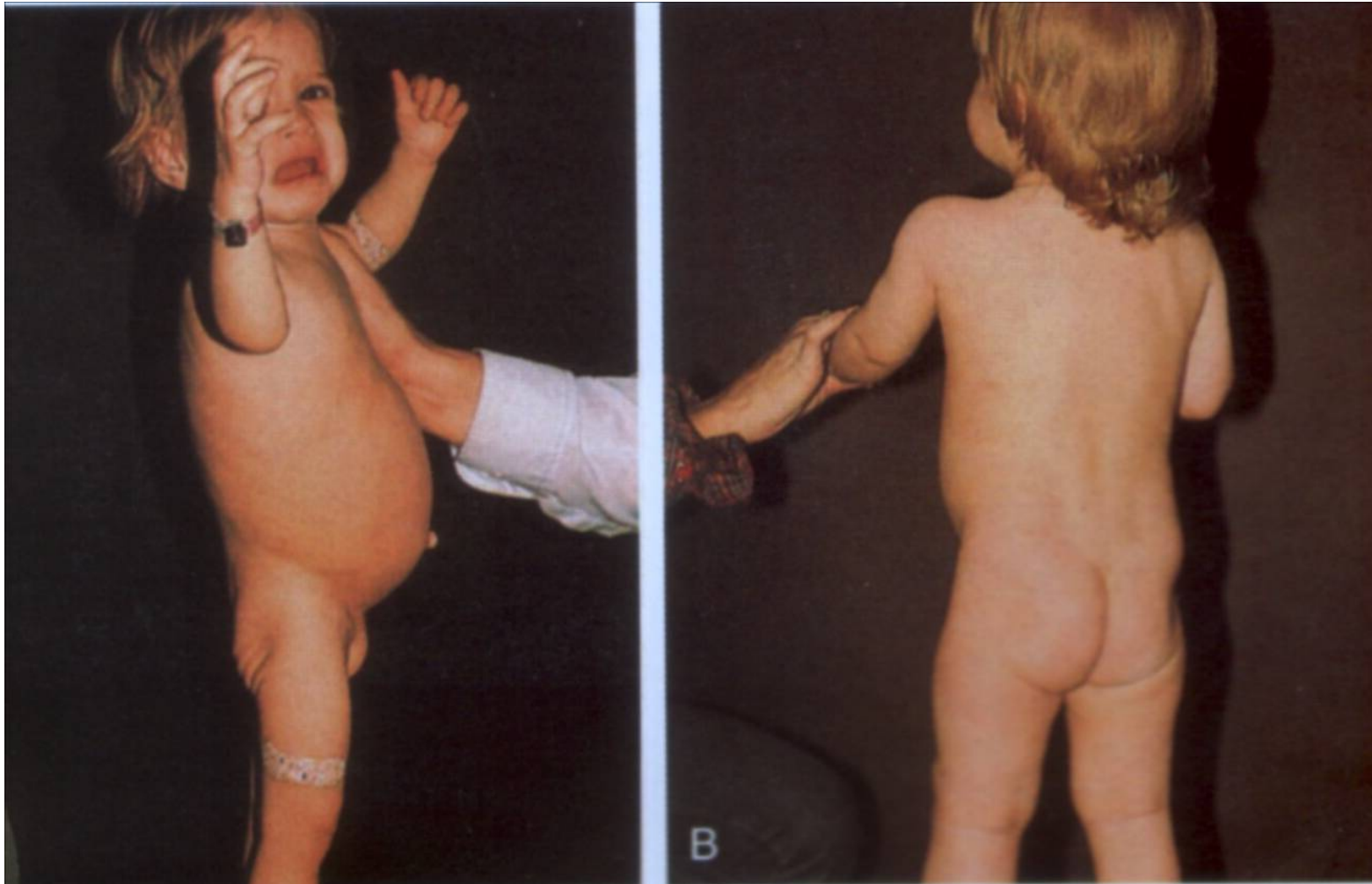


London, year 1938



GLUTEN DIET

AFTER GFD FOR
10 WEEKS



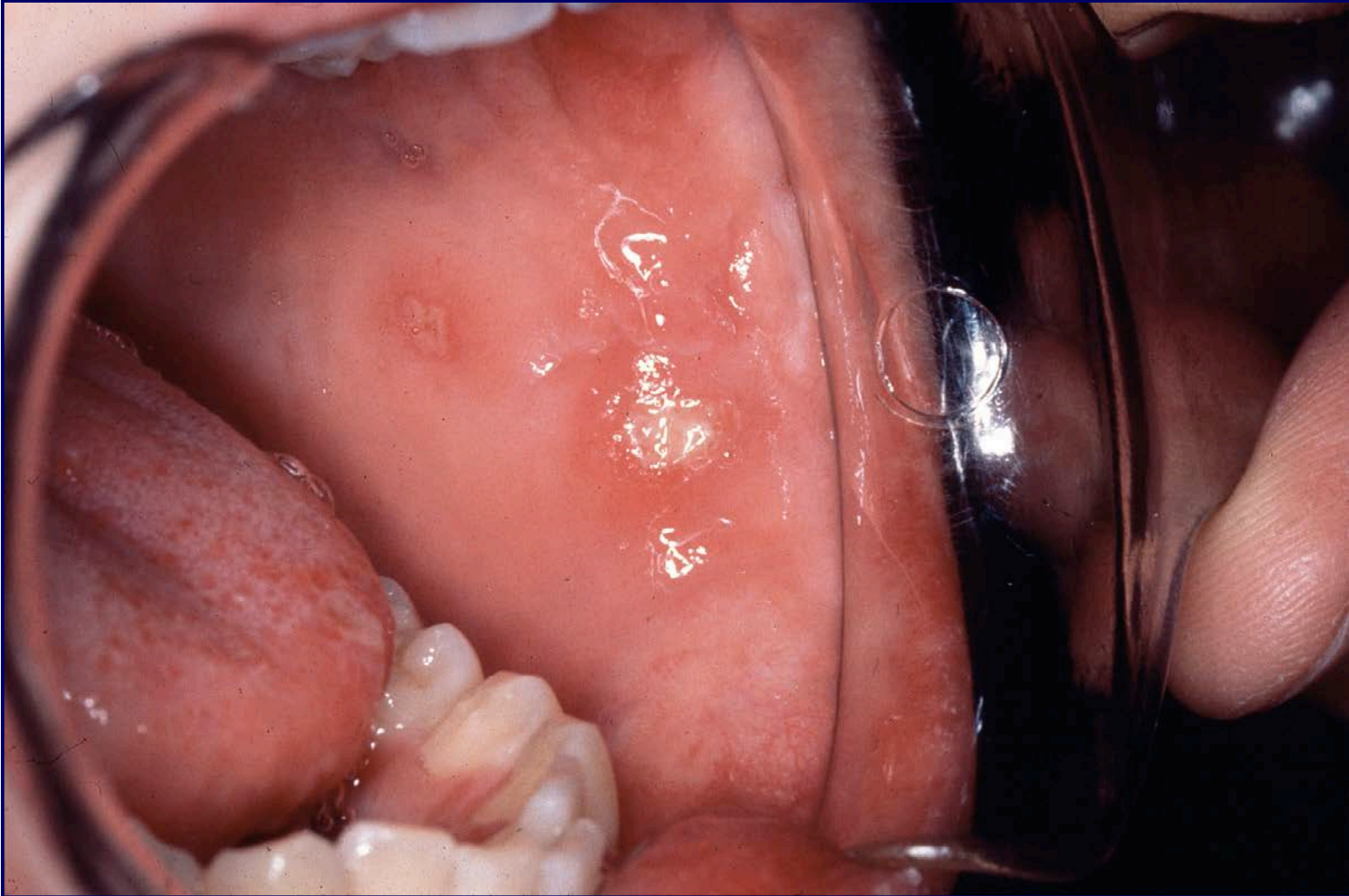
UNCOMMON PRESENTATION

- Secondary (?) to malabsorption
 - Anemia, fatigue
 - Vitamin deficiencies
 - Muscle wasting
 - Osteopenia
 - Short stature
 - Recurrent abortions / infertility
 - Delayed puberty
 - Dental enamel hypoplasia
 - Dermatitis Herpetiformis
 - Aphthous ulcers

(NIH, 2004; Fasano, 2005)



APHTHOUS ULCERS



DENTAL ENAMEL DEFECTS



DERMATITIS HERPETIFORMIS



Erythematous macule >
urticarial papule > tense
vesicles

Severe pruritus

Symmetric distribution

90% no GI symptoms

75% villous atrophy

Gluten sensitive



Other Problems to take into consideration

○ Silent celiac disease

- Children who are asymptomatic but have + serologic tests and villous atrophy
 - Autoimmune response present but no outward symptoms
 - Low-intensity symptoms often present (Fasano, 2005)

○ Latent celiac disease

- Children who have a + serology but no intestinal mucosal changes. They may have symptoms or mucosal changes in the future.

○ Refractory celiac disease

- Persistent symptoms despite gluten-free diet



DIFFERENTIAL DIAGNOSIS

- Anorexia nervosa
- Autoimmune enteropathy
- Bacterial overgrowth
- Collagenous sprue
- Crohn's disease
- Giardiasis
- Human immunodeficiency virus enteropathy
- Hypogammaglobulinemia
- Infective gastroenteritis
- Intestinal lymphoma
- Irritable bowel syndrome
- Ischemic enteritis
- Lactose intolerance
- Pancreatic insufficiency
- Soy protein intolerance
- Tropical sprue
- Tuberculosis
- Whipple's disease
- Zollinger-Ellison syndrome



DIAGNOSIS OF CELIAC DISEASE

○ Serology

- Serum immunoglobulin A (IgA) endomysial antibodies and IgA tissue transglutaminase (tTG) antibodies. Sensitivity and specificity > 95%.
- Testing for gliadin antibodies is no longer recommended because of the low sensitivity and specificity for celiac disease.
- The tTG antibody test is less costly because it uses an enzyme-linked immunosorbent assay; it is the recommended single serologic test for celiac disease screening in the primary care setting.
- When the prevalence is low, as in the general U.S. population, the risk of a false-positive result is high even with an accurate test . PPV 49.7%, NPV 99.9%
- IgA deficiency can give false negative
- Confirmatory testing, including small bowel biopsy, is advised.



SMALL BOWEL BIOPSY

- Required to confirm the diagnosis of celiac disease for most patients.
- Should also be considered in patients with negative serologic test results who are at high risk or in whom the physician strongly suspects celiac disease.
- Mucosal changes may vary from partial to total villous atrophy, or may be characterized by subtle crypt lengthening or increased epithelial lymphocytes.
- To avoid false-negative results on endoscopic biopsy, most authorities recommend obtaining at least four tissue samples, which increases the sensitivity of the test.



TREATMENT OF CELIAC DISEASE

- Avoidance of food products that contain gluten proteins.
- It is essential that the diagnosis be confirmed before submitting patients to this therapy.
- Key elements to successful treatment include the motivation of the patient, the attentiveness of the physician to comorbidities that need to be addressed.
- Formal consultation with a trained dietitian is necessary.
- The dietitian plays a vital role in helping the patient successfully adapt to the necessary behavioral changes and may provide much of the required follow-up.
- National celiac disease support organizations can provide patients invaluable resources for information and support.



TREATMENT FOR CELIAC DISEASE

- Gluten contained in wheat, rye, barley
 - Triticale, kamut, spelt, semolina, farina, einkorn, bulgur, and couscous
 - Malt made from barley
 - Malt syrup, malt extract, malt flavoring, malt vinegar
 - Beer, whiskey
 - Food additives
 - Soy sauce, carmel color, bouillon, modified food starch
 - Mono or diglycerides, emulsifiers, vegetable protein
 - Processed foods
 - Sausage, luncheon meat, gravies and sauces
 - TV dinners, pot pies



TREATMENT FOR CELIAC DISEASE

- Nutritional deficiencies with CD
 - B vitamins, iron, and folic acid
 - 4% anemia at time of diagnosis
 - GF foods not enriched
 - Low in B vitamins, calcium, vitamin D, iron, zinc, magnesium, and fiber
 - High incidence of osteopenia in children
 - Other food sensitivities and allergies common
 - May resolve with treatment of CD



TREATMENT FOR CELIAC DISEASE

- Monitor growth and development
- Secondary lactose intolerance common until gluten-free diet > 6 months
- Supplemental vitamins
 - Iron, folate
 - Calcium
 - Fat soluble vitamins
- Bone density studies
- Re-measure tTGA after 6-12 months of treatment
 - ↓ antibody titer if on GFD
 - Antibody levels return to normal within three to 12 months of starting a gluten-free diet.
 - Reaffirm need for GFD



THE CELIAC DIET

Table 6. Gluten Content of Some Common Foods

<i>Category</i>	<i>Contains gluten</i>	<i>Usually gluten free</i>
Breads, cereals, rice, and pasta	Bread or pasta made from barley, bran, gluten flour, graham flour, oat bran,* rye, wheat-based semolina, spelt, wheat, or wheat germ Cereals made with wheat, rye, barley, or oats,* or with malt extract or malt flavorings	Bread, cereals, or pasta made from arrowroot corn, buckwheat, corn, cornmeal, hominy, millet, potato starch, rice, rice bran, sago, soy, or tapioca Puffed corn Rice (brown or white); rice noodles
Vegetables and beans	Creamed or breaded vegetables; some French fries Canned baked beans	Plain, fresh, frozen, or canned vegetables Soybeans
Fruits	Some commercial fruit pie fillings and dried fruit	All fruits
Dairy	Malted milk; some milk drinks and flavored or frozen yogurt	Milk and milk products that do not contain gluten additives
Meat, poultry, fish, shellfish, eggs, and nuts	Any prepared with barley, oats, rye, wheat, or gluten stabilizers or fillers, including some cold cuts, frankfurters, sandwich spreads, sausages, and canned meats	Plain meat, poultry, fish, and shellfish Cold cuts, frankfurters, sandwich spreads, and sausages that do not contain gluten fillers Eggs; nuts and peanut butter
Snacks and condiments	Many commercial salad dressings, prepared soups, condiments, and sauces	Butter and margarine Honey; jam and jelly; molasses; sugar Coconut; hard candy; marshmallows; meringue; plain chocolate
Beverages	Flavored instant coffees; herbal teas Hot cocoa mixes; nondairy cream substitutes	Pure instant or ground coffee; tea Carbonated drinks; fruit juices

*—Pure oats are usually well tolerated but patients should be cautioned that oat products are frequently contaminated with gluten during processing.

NOTE: This is not a complete list. Patients should read food labels to confirm that food is gluten free. Patients should also check with their pharmacists because some medications contain gluten.

Information from reference 22.



THE CELIAC DIET



RESOURCES

○ Gluten-free cooking

- Gluten-free online recipes

www.glutenfreeda.com

- Whole Foods gluten-free shopping list

<http://www.wholefoods.com/healthinfo/gluten.pdf>

- *Gluten-Free Gourmet* by Betty Hagman

○ Google Celiac Support Groups

<http://www.enabling.org/ia/ceeliac/groups/groupsus.html>

<http://www.nowheat.com/grfx/nowheat/primer/celisoc.htm>



RESOURCES

- Celiac Sprue Association of the USA
www.csaceliacs.org
- Celiac Disease Foundation
www.celiac.org
- Gluten Intolerance Organization
www.gluten.net
- National Foundation for Celiac Awareness
www.celiacawareness.org
- Canadian Celiac Association
www.celiac.ca
- Columbia Celiac Disease Center
www.celiacdiseasecenter.columbia.edu



REFERENCES

- Guandalini, S. Essential Pediatric Gastroenterology, Hepatology, & Nutrition. MC 2005, 221-230.
- Schuppan, D, Deiterich, W 2009. Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults. Retrieved 10/15/09, from Up To Date website:
http://www.utdol.com/online/content/topic.do?topicKey=mal_synd/5090&selectedTitle=2~150&source=search_result
- Guandalini, S (2009 Sep 2). Celiac Disease. Retrieved 10/20/09, from Emedicine.medscape website:
<http://emedicine.medscape.com/article/932104-overview>

