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Celiac Disease

Isabel Polanco

Department of Paediatric Gastroenterology and Nutrition, Hospital Infantil Universitario La Paz, Facultad de Medicina, Universidad Autónoma, Madrid, Spain

ABSTRACT

Celiac disease is an immunologically mediated enteropathy of the small intestine, characterized by lifelong intolerance to the gliadin and related prolamines from wheat and other cereals, that occurs in genetically predisposed individuals. Symptoms result from structural damage to the mucosa of the small intestine, which may cause malabsorption with positive autoantibodies in the sera. Normal mucosal architecture is restored after the use of a gluten-free diet and the normalization of the autoantibodies. Villous atrophy and high levels of autoantibodies reappear when gluten is reintroduced into the diet (gluten challenge). ***JPGN 47:S3–S6, 2008.*** **Key Words:** Celiac disease—Genetic—Gluten—Immunologic factors. © 2008 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

EPIDEMIOLOGY

The true incidence of celiac disease (CD) in susceptible populations may be dramatically higher than has been previously recognized (1–4). Most cases remain undiagnosed unless actively identified through mass serological screening. CD affects female individuals more than male individuals (ratio 2:1). A relationship between a diagnosis of CD and various factors (genetic background, quality and quantity of gluten, age at introduction of gluten, and breast-feeding) has been described (5–7).

GENETIC FACTORS

The primary association of CD is the HLA-DQ dimer DQA1∗0501/DQB1∗0201. The majority of patients and first-degree relatives (and ≤20% of normal control individuals in susceptible populations) may express this dimer on antigen-presenting cells. The possession of this haplotype is not enough to cause gluten-induced changes, and the administration of extra gluten to HLA-identical siblings of CD patients does not always result in pathological changes to the intestine. The HLA-DQ dimmer is also strongly linked to HLA-DR status (8).

Address correspondence and reprint requests to Isabel Polanco, MD, PhD, Department of Paediatric Gastroenterology and Nutrition, Hospital Infantil Universitario La Paz, Universidad Autónoma, Madrid, Spain (e-mail: med012403@nacom.es).

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PATHOLOGY

The proximal mucosa of the small intestine in patients with CD becomes abnormal on gluten ingestion, and small bowel biopsy is essential to confirm the diagnosis. The abnormality is characterized by stunted villi or even absence of villi associated with an increase in crypt length and cell numbers—the so-called flat mucosa. The flat gut lesion is characteristic of CD but is nonspecific (Table 1). Figure 1 (9).

All structural damage resolves on gluten withdrawal but recurs if gluten is reintroduced to the diet. Similar intestinal changes are frequently found in dermatitis herpetiformis, an intensely itchy, chronic, papulovesicular skin disorder caused by granular subepithelial IgA deposits in the upper dermis. Both the cutaneous and the

TABLE 1. *Causes other than CD that may produce flattened jejunal mucosa*

Children
Transient gluten intolerance
Soy and cow protein enteropathy
Autoimmune enteropathy
Acute viral enteritis
Giardiasis
Prolonged malnutrition
Adults
Zollinger-Ellison syndrome
Tropical sprue
Giardiasis
Oral contraceptives
Other

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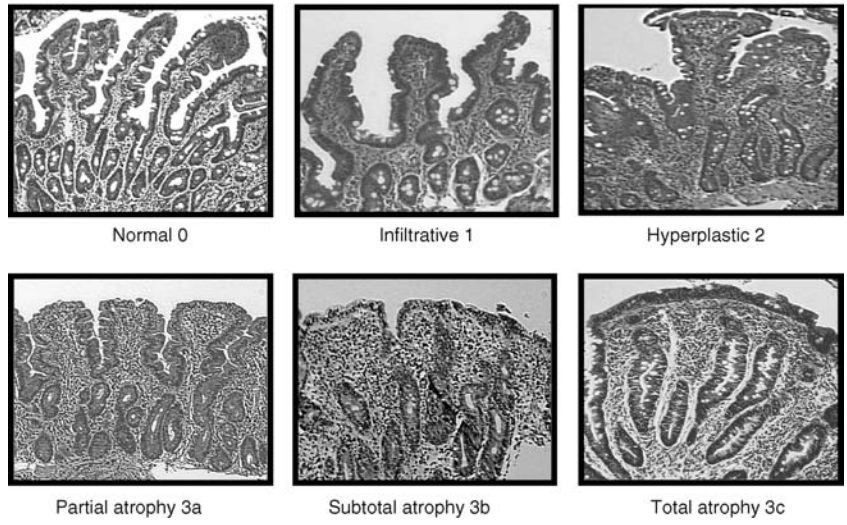

FIG. 1. Histological features of CD.

TABLE 2. *Clinical presentation of CD according to age at onset of symptoms*

Symptoms	Signs
Classic presentation	
Chronic diarrhea	Abdominal distension
Anorexia	Buttock wasting
Abdominal distension	Malnutrition/growth failure
Weight loss	Pallor
Vomiting	Irritability
Irritability/lethargy	Psychomotor delay
	Hematomas
	Rickets
Presentation at older age	
Asymptomatic	Glossitis, aphthous ulcers
Absence of diarrhea	Short stature
Decreased appetite	Iron deficiency anemia
Anorexia	Osteopenia
Growth failure	Bruising
Pubertal delay	Arthritis/arthralgia
Menstrual irregularities	Enamel hypoplasia
Abnormal (loose) stools	Cerebral calcifications
Arthritis/arthralgia	
Abdominal pain	
Constipation	
Presentation at adulthood	
Anxiety/depression	Glossitis, aphthous ulcers
Chronic diarrhea	Malnutrition
Anorexia	Spontaneous hemorrhage
Abdominal pain	Peripheral edema
Infertility	Isolated megaloblastic anemia
Paresthesias	Cramps/tetany
Nocturnal diuresis	Digital clubbing
Bone pain	Proximal myopathy
Cerebrospinal degeneration	Peripheral neuropathy
	Variety of rashes
	Hyposplenism

intestinal lesions regress with a gluten free-diet. Dermatitis herpetiformis is now considered to be a specific skin manifestation of CD.

CLINICAL FEATURES

Celiac disease can have different clinical manifestations.

In general, the first symptoms appear during the months after the introduction of gluten in the diet. The earlier gluten is introduced, the shorter the interval between introduction and occurrence of the first symptoms. The first symptoms of CD, therefore, traditionally occur between 12 months and 3 years of age (Table 2).

In a minority of children, diagnosis is not made by the age of 5 years. CD can therefore be diagnosed at any time up to adulthood, because symptoms have been either ignored or misinterpreted (eg, short stature), because the

TABLE 3. *Associated disorders in 1010 children with CD at the Hospital Infantil Universitario La Paz, Madrid (Spain)*

Selective IgA deficiency	37	Down syndrome	3
Dermatitis herpetiformis	36	Cardiac disease	3
Diabetes mellitus	32	Thyroid disorders	3
Bronchial asthma	6	Cystic fibrosis	1
Psoriasis	6	Fibrosing alveolitis	1
Chronic active hepatitis	6	Renal tubular acidosis	1
Epilepsy	6	Spinocerebellar degeneration	1
Vitiligo	4		
Total = 146			

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TABLE 4. *Mode of presentation in 1010 children with CD at the Hospital Infantil Universitario La Paz, Madrid (Spain)*

Retarded growth	90	Bleeding	23
Anemia	79	Edema	20
Constipation	72	Aphthous stomatitis	8
Abdominal pain	57	Epilepsy	6
Abdominal distension	46	Ataxia	4
Muscular hypotony	25		

Classic presentation (eg, chronic diarrhea, abdominal distension, failure to thrive, anorexia): 580 cases (57.4%).
Atypical presentation: 430 cases (42.6 %).

disease is truly symptomless, or when some other autoimmune disease occurs (Tables 3 and 4).

Latent Celiac Disease

Individuals with CD may present with a severe or mild enteropathy at different times of their life. In fact, some individuals have had normal jejunal biopsy results while taking a normal diet but at some other time have had a flat jejunal biopsy specimen and recovered while using a gluten-free diet. For such individuals, the definition of latent CD has been proposed. This definition can also be applied to ''late relapsers'' (10–12).

DIAGNOSIS

The diagnosis of CD requires both a jejunoduodenal biopsy specimen that shows the characteristic findings of intraepithelial lymphocytosis, crypt hyperplasia, and villous atrophy (Figure 1) and a positive response to a gluten-free diet. The diagnostic criteria developed by the European Society for Pediatric Gastroenterology and Nutrition (2) require only clinical improvement with the diet, although histological improvement with a gluten-free diet is frequently sought and is recommended for adults because villous atrophy may persist despite a clinical response to the diet. In most patients, the diagnosis is easily established. However, roughly 10% of cases are difficult to diagnose because of a lack of concordance among the serological, clinical, and histological findings (1–3).

TABLE 5. *Serological tests for CD*

Test	Sensitivity	Specificity	PPV	NPD
AGA IgG	57–100	42–98	20–95	41–88
AGA IgA	53–100	65–100	s28–100	65–100
AEA IgA	75–98	96–100	98–100	80–95
Guinea pig tTG	90.2	95		
Human tTG	98.5	98		

NPD = negative predictive value; PPV = positive predictive value.

The most sensitive antibody tests for the diagnosis of CD are of the IgA class. The recognition that the enzyme tissue transglutaminase is the autoantigen for the development of endomysial antibodies has allowed the development of automated enzyme-linked immunoassays that are less expensive than the endomysial antibody test. Overall, the sensitivity of the tests for both endomysial antibodies and anti–tissue transglutaminase antibodies is greater than 90%, and a test for either marker is considered the best means of screening for CD (Table 5). The titers of endomysial antibodies and anti–tissue transglutaminase antibodies correlate with the degree of mucosal damage; as a result, the sensitivity of these antibody tests declines when a greater number of patients with lesser degrees of villous atrophy are included in studies. The various commercially available assays for anti–tissue transglutaminase antibodies have different characteristics and resultant sensitivities and specificities.

TREATMENT

A strict gluten-free diet with lifelong exclusion of gluten from wheat, rye, barley, and oats must be recommended for both symptomatic and asymptomatic individuals. Lifelong adherence to a strict gluten-free diet should be advised for all children with CD to avoid the late complications of the disease (13). Adherence to a strict gluten-free diet is essential but not easy, and follow-up monitoring by a gastroenterologist about once a year seems to be advisable. CD patients' associations help patients to adhere to a gluten-free diet and to understand their disease better.

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