CASE 42
CELIAC DISEASE

Chronic tissue damage in the gut caused by hypersensitivity to a common food antigen.

Celiac disease (also known as gluten-sensitive enteropathy) is an immune-mediated inflammatory disease of the gastrointestinal tract caused by a permanent sensitivity to gluten, the primary protein present in wheat, barley, and rye. Gluten is degraded into antigenic peptides that trigger an immunologic process in the gut that leads to diarrhea, malabsorption, and, ultimately, nutritional deficiencies and failure to thrive. There is a description of celiac disease dating back to the 1st century AD, but it was not until the 20th century that the trigger for the disease was identified. Willem Karel Dicke, a Dutch pediatrician, noted that children with celiac disease had a clear improvement in their symptoms during the Second World War, when cereals were scarce. After the war and the reinstatement of cereals in their diet, children with celiac disease relapsed, and wheat was recognized as the major culprit.

Celiac disease is perhaps the most common genetic disorder, with a prevalence of 0.5–1.0% in white populations. The principal genetic determinants of the disease have been identified as the highly variable HLA class II *DQA1* and *DQB1* genes in the major histocompatibility complex. The genes *DQA1*05xx* with *DQB1*02xx* encode HLA molecule DQ 2.5 and *DQA1*03xx* with *DQB1*0302* encode DQ8. Notably, between 92 and 100% of patients with celiac disease have these allele pairs. Celiac disease is singular among immunologic diseases in that the exogenous antigen, the autoantigen, and the genetic susceptibility have all been clearly described, and therefore it provides a useful model for studying the genesis of immunologically mediated diseases.

This case was prepared by Raif Geha, MD, in collaboration with MaryBeth Son, MD.

TOPICS BEARING ON THIS CASE:

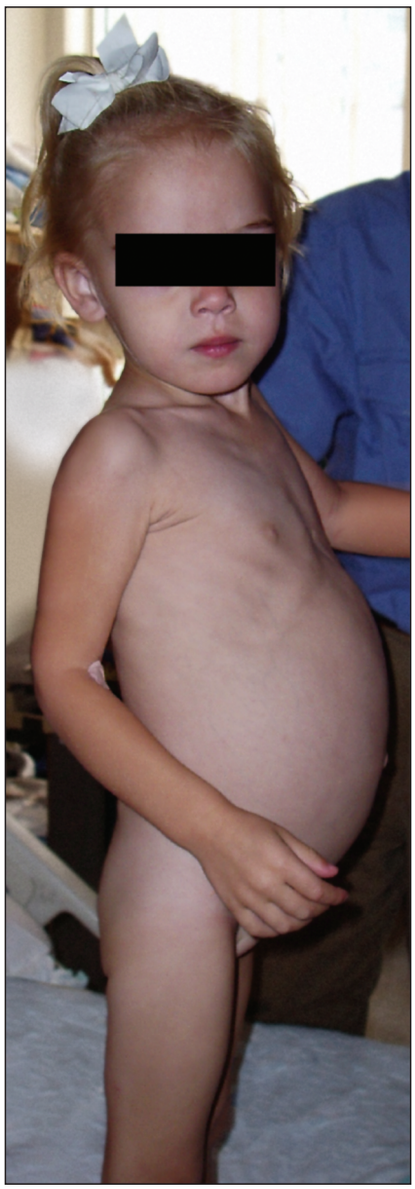
- Gut mucosal immune system
- Allergy and hypersensitivity

Demeter O'Reilly: a little girl who lost weight and became weak.

Tests for celiac disease positive.

Demeter O'Reilly was a healthy baby who grew normally until 12 months old, when her parents noticed that she became irritable and stopped gaining weight. She was observed closely by her pediatrician for the next 3 months during which time she developed a distended abdomen, passed large, foul-smelling stools, and lost nearly 2 kg in weight. Her parents also noticed that Demeter was becoming progressively weaker.

At birth, Demeter weighed 3.8 kg, was 52 cm long, and had a head circumference of 36 cm (all within the normal range). Both of her parents were of Irish American ancestry and were healthy, as was her 3-year-old sister. There was no known history of metabolic, neurologic, or gastrointestinal disease in children in the family. There was no history of autoimmune diseases, including type 1 diabetes mellitus or autoimmune thyroid disease.



Given the progression of her symptoms and the weight loss, Demeter was referred to the Children's Hospital Emergency Room at 15 months. When she arrived she appeared pale and chronically ill. She weighed 8.5 kg (5th centile), her height was 77.5 cm (50th centile), and her head circumference was 46 cm (50th centile). The examination made Demeter fretful but she could be consoled. She was mildly dehydrated, and had a protuberant abdomen and significant muscle wasting in her buttocks, legs, and arms (Fig. 42.1). No enlargement of liver, spleen, or lymph nodes was evident.

Laboratory tests revealed anemia, with a hemoglobin level of 10 g dl^{-1} (normal 12–14 g dl^{-1}). Her white-cell count and platelets were normal. She had a mild elevation of liver enzymes (transaminitis), with aspartate aminotransferase at 48 U l^{-1} (normal range 2–40 U l^{-1}) and alanine aminotransferase at 46 U l^{-1} (normal range 3–30 U l^{-1}). Her albumin was normal at 3.7 g dl^{-1}. No evidence of metabolic disease was found. Serologic samples for testing for celiac disease were sent to the laboratory. Demeter tested positive for anti-endomysium IgA antibodies (autoantibodies against the connective tissue that sheathes muscle—the endomysium) at a titer of 1:2560 and for anti-tissue transglutaminase (TTG) IgA antibodies at a level greater than 118 U ml^{-1} (greater than 25 U ml^{-1} is considered positive).

Given Demeter's symptoms and the positive serologic results, the decision was made to perform a biopsy of her gastrointestinal tract. An upper gastrointestinal endoscopy revealed edema and flattening of the mucosal folds in the duodenal bulb. Multiple biopsies were taken from the distal duodenum and duodenal bulb. Review of the pathology of the tissues showed subtotal to total villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes (Marsh type 3 lesion) (Fig. 42.2). The clinical presentation, serology, and biopsy results confirmed the diagnosis of celiac disease.

Demeter's family received extensive nutritional counseling and she was started on a gluten-free diet. At the 6-month follow-up, she was doing extremely well, with an excellent energy level. She had normal bowel movements once a day and had no abdominal pain or vomiting. Her weight was now in the 75th centile and her height was at the 50th centile for her age. She appeared a robust and healthy toddler with a normal abdomen and muscle bulk. Serologic tests revealed no anti-endomysium

Fig. 42.1 A child with celiac disease. Note the protuberant abdomen, muscle wasting, and malnourished appearance. Photograph courtesy of Dascha Weir.

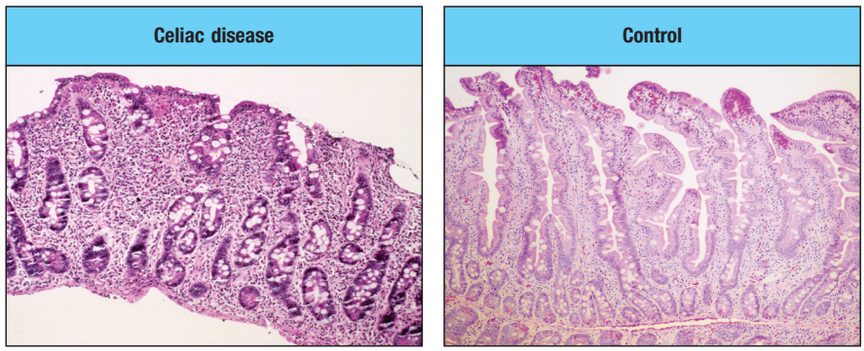


Fig. 42.2 Comparison of mucosal tissue taken by internal biopsy from a patient with celiac disease and from a healthy intestine. The tissue from the patient with celiac disease is on the left, the healthy tissue on the right. Note the flattened mucosal surface, crypt hyperplasia, and extensive inflammatory infiltrate in the celiac disease biopsy. Photograph courtesy of Donald A. Antonioli.

and anti-TTG antibodies. Her family had availed themselves of the many sources of advice and support available to families with celiac disease, and felt comfortable with her gluten-free diet.

Multiple biopsies from duodenum performed, as inflammation can be patchy.

Celiac disease.

The prevalence of celiac disease, or gluten-sensitive enteropathy, varies by population, and it has been estimated that 0.5–1.0% of the general population in Europe and the United States are affected. However, variability in presentation and delay in onset of symptoms probably lead to the disease being under-diagnosed. Although the classic description of the disease is in very young children, celiac disease presents most commonly between the ages of 10 and 40 years. The disease clusters in families, and as noted above, the HLA molecules DQ2 and DQ8 are necessary but not sufficient for the development of celiac disease. First-degree relatives of affected patients have a 10–15% prevalence, although many of these patients may have unrecognized disease. In addition, patients with type 1 diabetes mellitus, Down syndrome (Trisomy 21), Turner syndrome (45,XO), Williams syndrome (congenital facial and cardiac abnormalities with hypercalcemia), autoimmune thyroiditis, or selective IgA deficiency are at higher risk than the rest of the population of developing celiac disease.

Children with celiac disease classically come to the physician's attention between 6 and 24 months of age with abdominal distension, diarrhea, malabsorption, and weight loss. Anemia, irritability, and muscular wasting are often observed. On rare occasions, children in celiac crisis are seen with severe diarrhea, dehydration, and marked disturbance in electrolyte balance; they require immediate treatment with intravenous corticosteroid. Older children may have more subtle symptoms but will also have diarrhea, nausea, vomiting, and abdominal pain. Interestingly, constipation is seen in about 8% of patients with celiac disease. Atypical features of the disease include hypoplasia of the enamel of the permanent teeth, osteopenia/osteoporosis, short stature, and delayed puberty. Dermatitis herpetiformis, an intensely itchy rash consisting of small solid papules and water-filled vesicles, is a dermatologic manifestation of celiac disease; small-bowel biopsies in patients with dermatitis herpetiformis reveal lesions that are consistent with gluten-sensitive enteropathy. Both the rash and the gastrointestinal lesions remit if gluten is removed from the diet.

Adults with celiac disease most commonly present with iron-deficiency anemia that does not respond to oral iron therapy. Gastrointestinal symptoms such as diarrhea and flatulence sometimes predominate. It is also important to consider celiac disease in patients with unexplained bone fractures, arthritis, transaminitis, or neurologic symptoms including peripheral neuropathy or ataxia, as well as in women with infertility.

The development of highly sensitive and specific serologic tests for celiac disease has greatly aided its diagnosis. Serologic tests are also indirect tests of adherence to a gluten-free diet, because celiac antibodies decrease and eventually become undetectable in most patients on a gluten-free diet. Several different serologic tests are in use. For initial screening, the current guidelines from the American College of Gastroenterology recommend testing for IgA anti-tissue transglutaminase (TTG) antibody for individuals over the age of 2 years (using second-generation ELISA technology, the sensitivity and specificity is >95% in untreated patients). Given the higher prevalence of IgA deficiency in the celiac population, many practitioners also send a total IgA level concomitantly. In patients with IgA deficiency, IgG TTG can be measured, but has limited specificity. IgG antibodies to deaminated gliadin peptides (DPG) can be sent with IgG TTG to increase diagnostic accuracy in patients with IgA deficiency. Anti-gliadin antibodies were used for decades but have been replaced given wide variability in their diagnostic accuracy. Testing for anti-endomysium IgA antibody is frequently used as it is also highly sensitive and specific, but measurement of this test is observer-dependent and it is more expensive than other tests. Positive titers of anti-TTG and anti-endomysium antibodies are almost 100% successful in predicting celiac disease lesions in symptomatic patients. Regardless of the serologic findings, all suspected cases should be confirmed by a biopsy of the small intestine. Characteristic pathology includes partial to total villous atrophy and lymphocyte infiltration with crypt hyperplasia in the small intestine. HLA typing for DQ2 and DQ8 is potentially helpful in cases with equivocal histopathology, as celiac disease is unlikely if neither is present.

Patients with clinical signs and symptoms of malabsorption, including chronic diarrhea with weight loss, steatorrhea, recurrent abdominal pain, chronic constipation, and bloating should be tested for celiac disease while on a gluten-rich diet. Other indications for testing include short stature, pubertal delay, refractory iron deficiency anemia, unexplained fractures, or recurrent aphthous stomatitis. Testing of asymptomatic individuals in high-risk groups, including first degree relatives of patients with celiac disease, patients with autoimmune thyroiditis and Type 1 diabetes mellitus, remains controversial as the benefits of screening for celiac disease in asymptomatic individuals haven't been clearly demonstrated. Nonetheless, guidelines from some societies, including the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, include these recommendations. Other groups considered at high risk for celiac disease include individuals with Down's syndrome, Turner syndrome, Williams syndrome, selective IgA deficiency, and autoimmune hepatitis.

The treatment for celiac disease is lifelong adherence to a gluten-free diet. All foods containing wheat, barley, and rye as well as their derivatives need to be completely eliminated from the diet. Oats in their pure form are likely tolerated in small amounts (approximately 2 oz per day), but there is a risk of cross contamination of oats with other gluten-containing grains during processing. As such, the introduction of oats into a gluten-free diet remains somewhat controversial. Foods that are labeled gluten-free per the FDA contain less than 20 ppm (parts per million) of gluten, as this is the lowest level that can be consistently detected in foods using valid scientific analytical tools. A gluten-free diet is challenging to comply with, is more expensive than a normal diet, and can impact social activities. As such, it is essential to give patients and their families extensive nutritional counseling as well as support in their endeavors to maintain the diet.

Untreated celiac disease leads to significant illness and an increased risk of mortality. Children with untreated celiac disease are at increased risk for problems with growth and decreased bone mineralization, which will correct on a gluten-free diet. Women with untreated celiac disease are more likely to have spontaneous abortions, babies of low birth weight, and a shorter duration of breastfeeding. Lastly, there is an increase in mortality due to cancer in adults with celiac disease, primarily enteropathy-associated T-cell lymphoma. Some studies suggest that strict compliance with a gluten-free diet may reduce the risk of cancer compared with those patients who do not comply.

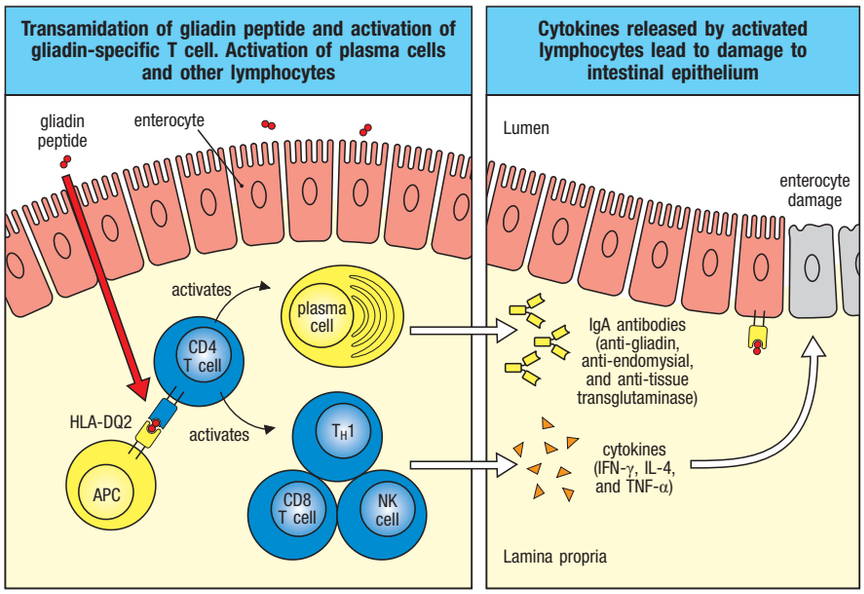


Fig. 42.3 The pathogenesis of celiac disease. Inflammation of the small intestine is caused by CD4 T cells responding to peptides derived from gluten that are deamidated by tissue transglutaminase and presented by HLA-DQ8 or HLA-DQ2 molecules. APC, antigen-presenting cell.

Given the difficulty and expense of a gluten-free diet as well as the prevalence of celiac disease, alternative, non-dietary treatments to a gluten-free diet are being explored. A recently published Phase II trial assessed the efficacy of glutenase ALV003 in decreasing biopsy findings of celiac disease by assessing the ratio of villus height to crypt depth and intraepithelial lymphocytic density. ALV003 is an orally administered mixture of two recombinant gluten-specific proteases. Biopsy results indicated that ALV003 was protective against gluten-induced mucosal damage. Symptoms didn't differ in treated versus placebo groups. Thorough evaluation of this and potentially other non-dietary treatments is required before any changes in the recommendations for a gluten-free diet can be given to patients with celiac disease.

Several aspects of the pathogenesis of celiac disease are now quite well understood. The exogenous antigen is gluten, a mixture of gliadin and glutenin polypeptides present in wheat. Ingested proteins are usually degraded into small residues by gastric, pancreatic, and intestinal enzymes during transit through the gastrointestinal tract. In most cases, these residues are not appropriate stimulators of the immune system because they are not big enough to bind HLA molecules. However, epitopes in gliadins with proline-rich residues, including a proline-rich peptide of 33 amino acids (A-gliadin), survive transit through the gastrointestinal tract and arrive intact in the small bowel. This peptide passes through the gastrointestinal lining into the subepithelial space. Such trafficking is usually prevented by the competent tight intercellular junctions of the gastrointestinal epithelium. A number of factors may damage the epithelial barrier, including infection, gluten-induced upregulation of zonulin (an intestinal peptide involved in the regulation of tight junctions), or mechanical stress. In the subepithelial space the peptides are modified by enzymes, and are picked up and presented by antigen-presenting cells to CD4 T cells, thereby initiating an inflammatory response that is self-perpetuating in the presence of gluten and damages the gastrointestinal tract (Fig. 42.3). The enzyme TTG deamidates the peptide, enhancing binding to HLA DQ2 and DQ8 on antigen-presenting cells, and has also been identified as an autoantigen in the disease (Fig. 42.4). The mechanism of formation of TTG autoantibodies is incompletely understood, and there is some controversy regarding the role of anti-TTG antibodies in the pathogenesis. However, it is clear that the interplay of these factors underpins the immune-mediated damage that is seen in patients with celiac disease.

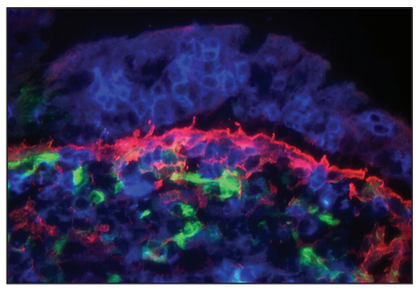


Fig. 42.4 Immunofluorescence staining of the mucosa of the small intestine from an untreated patient with celiac disease. Tissue transglutaminase (TTG, pink), HLA-D (green), and T cells (CD3, purple) have been specifically stained for. Note the close spatial relationship between TTG, the antigen-presenting cells expressing HLA-DQ, and T cells just beneath the intestinal epithelium.

After presentation of the immunogenic peptides to CD4 T cells, an inflammatory response is initiated that is characterized by a CD4 T_H1 response, with interferon-γ (IFN-γ) as the predominant cytokine. It is likely that some of the intestinal damage is mediated via a bystander effect of IFN-γ, but there may be other mechanisms involved. Examination of gastrointestinal lesions in patients shows infiltration of the intestinal mucosa by both CD4 lamina propria lymphocytes and intraepithelial CD8 T cells. As described above, there is significant evidence for the role of CD4 cells, but the role of the CD8 cells remains elusive.

The innate immune system may also be stimulated by gluten. There is evidence that gluten-derived peptides induce the release of IL-15 by intestinal epithelial cells. IL-15 activates antigen-presenting dendritic cells in the lamina propria and also leads to upregulation of expression of the cell-surface protein MIC-A by epithelial cells. Potentially cytotoxic CD8 intraepithelial lymphocytes in the mucosal epithelium can be activated via their NKG2D receptors, which recognize MIC-A, and they then kill MIC-A-expressing epithelial cells. These innate immune responses may create some intestinal damage and may also induce the co-stimulatory molecules necessary for initiating an antigen-specific CD4 T-cell response to other parts of the α-gliadin molecule. The ability of gluten to stimulate both innate and adaptive immune responses may explain its unique ability to induce celiac disease.

Questions.

1 *Given the high prevalence of celiac disease and the difficulty in maintaining a gluten-free diet, are there any new therapies on the horizon for this condition?*

2 *What are the current recommendations regarding screening of first-degree relatives and high-risk groups for celiac disease?*

3 *How is a food determined to be gluten free?*

4 *Can patients with celiac disease eat oats?*