Q&A

Celiac Disease: Hard to Handle

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Celiac disease (CD) is a disorder characterized by chronic small intestinal inflammation in response to gluten found in wheat, rye and barley. Epidemiological studies from the last decade have shown that CD is much more common than previously thought and that a large number of patients with CD will not have GI symptoms. The classic features on small bowel biopsy includes villous atrophy and crypt hyperplasia. There is clinical and histological improvement following a gluten-free diet and clinical and histological relapse when gluten is reintroduced.

Q&A *What is the epidemiology?*

Given the highly variable presentation of CD, the true prevalence is probably still unknown. Prevalence rates vary depending on the criteria used to defined CD (*i.e.*, serology with or without histological changes on biopsy). CD shows a geographical variation with the highest prevalence in Western Europe and in countries where Europeans have migrated, such as North America and Australia. The prevalence of CD is approximately 1%.[1,2]

Q&A *What is the clinical presentation?*

The clinical presentation of CD is highly variable. In infants and children, it can manifest as:

- failure to thrive,
- GI symptoms of vomiting,
- abdominal pain,
- bloating or diarrhea and/or
- features of anemia.

In adults, it can present with the classic symptoms of malabsorption (diarrhea and weight loss), or more commonly, as atypical CD (Table 1).

Table 1

Features of atypical celiac disease (CD) and complications

- Iron deficiency anemia
- Osteoporosis
- Elevated liver transaminases
- Arthralgia
- Polyneuropathy
- Ataxia
- Epilepsy
- Infertility
- Anxiety
- Depression
- Non-Hodgkins lymphoma
- Squamous cell carcinoma of the oropharynx and esophagus
- Adenocarcinoma of the small intestine

Table 2
Associated conditions of CD

- Dermatitis herpetiformis
- Type 1 diabetes mellitus
- Autoimmune thyroid disease
- Addison's disease
- Sjogren's syndrome
- Microscopic colitis
- Rheumatoid arthritis
- Down syndrome
- IgA nephropathy

Often, these atypical features may be the only clues that CD is present. The term "atypical CD" is misleading as the majority of adults have few, if any, GI symptoms and are diagnosed on the basis of a non-GI presentations, such as iron deficiency or osteoporosis. Furthermore, individuals can have "silent disease" with no symptoms except for histologic changes of CD.

Q&A *What are the associated conditions of CD?*

CD is associated with several other disorders, including dermatitis herpetiformis, other autoimmune disorders and IgA deficiency (Table 2). CD is also more common in individuals with Down syndrome.[3]

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Q&A *Are there any complications?*

Patients with CD are at higher risk for non-Hodgkin lymphoma (NHL), both intestinal and extraintestinal, compared to the general population. Other malignancies are described in Table 1.

Q&A *What is the pathophysiology?*

Gluten is a protein derived from wheat, barley and rye. The specific peptide sequences that can trigger the immune response are variable. One of the most studied is a 33-amino acid peptide.[4] This peptide passes through the barrier of the small intestine mucosa intact and interacts with antigen-presenting cells resulting in immune activation. Almost all (95% to 99%) individuals with CD express the major histocompatibility complex HLA-DQ2 or HLA-DQ8.

Q&A *What is the pathology?*

The Marsh system is used to grade the histological damage of CD. Marsh I is the earliest lesion and is defined by an increase the number of intraepithelial lymphocytes. Marsh II is characterized by hyperplasia of the crypts, while Marsh III is the classic villous atrophy with crypt hyperplasia and Marsh IV is a severe disease with a complete flattening of the mucosa. This is a major change in how we view CD, since it has only been in the last 20 years or so that these different grades of CD have been recognized. Prior to that, only Marsh III or IV was characterized as CD. There has been a lag in the introduction of

the grading system and (even 10 years ago) it was not uncommon that those with Marsh I and II CD were not diagnosed as CD by pathologists.

Q&A How is the diagnosis made?

The first step in the diagnosis of CD is to consider the possibility that the patient may actually have the disease. In patients suspected of having CD, IgA tissue transglutaminase antibody (tTGA) or IgA antiendomysial antibody (EMA) are recommended as the first test for CD.[5] Both EMA and tTGA have a sensitivity of > 90% and a specificity of > 95% (defined in Marsh III patient populations).[6] However, the sensitivity of these tests is reduced (in some cases it falls below 60%) in milder histological grades of CD (*i.e.*, Marsh I and II, which can make up 10% to 30% of all celiac patients). Since these antibodies are of the IgA class and IgA deficiency is found in 3% to 5% of patients with CD, an IgA measurement can reduce the risk of false-negative tTGA or EMA.[6] These tests normalize following the introduction of a gluten-free diet. A time lag for these tests to normalize is variable.

Duodenal biopsy

Duodenal biopsy examination remains the gold standard for establishing the diagnosis of CD and should be performed in all patients with a positive serologic test. Furthermore, negative celiac serology should not preclude duodenal biopsy examinations in those that are suspected of having CD. Patients who have a positive serologic test, but who have not undergone upper endoscopy, should be instructed to continue normal gluten consumption prior to the biopsy. If the patient has already started on a gluten-free diet then gluten should be reintroduced for two to four weeks prior to biopsy. A repeat biopsy is not necessary after diagnosis in patients who are improved on a gluten-free diet.

Table 3

Possible etiologies for non-improvement or relapse of CD

- Gluten ingestion
- Bacterial overgrowth
- Lactose intolerance
- Microscopic colitis
- Irritable bowel syndrome
- Inflammatory bowel disease
- Pancreatic insufficiency
- Refractory sprue
- Ulcerative jejunoileitis
- Lymphoma

The highest prevalence of CD is in Western Europe and in countries where Europeans have migrated, such as North America and Australia.

Q&A Who should be tested?

Individuals with GI symptom, such as chronic diarrhea and weight loss, should be tested. As well, given that CD is a multisystemic disease, FPs should consider CD in patients who otherwise have unexplained elevated transaminases, iron deficiency, infertility, Down syndrome or who have conditions associated with

Take-home message

- CD is a common condition
- A large number of patients with CD will present with atypical features or may have "silent disease"
- Tissue transglutaminase antibody and antiendomysial antibody serological testing can be falsely negative in the setting of IgA deficiency or milder histological grades (Marsh grade I and II) of CD
- Consider testing patients with atypical features or conditions associated with CD
- Treatment is life-long adherence to a gluten-free diet

CD. First-degree relatives of patients with CD should also be screened.

Q&A *What is the treatment?*

A gluten-free diet excluding wheat, rye and barley should be adhered to for life. Since many foods contain hidden gluten, a consultation with a dietitian is recommended. Oats are safe to ingest but commercial products may be contaminated with gluten.[7] Most patients will see some improvement in their clinical symptoms within six weeks of initiating a gluten-free diet. The most common causes for lack of improvement or relapse are described in Table 3.

CD is associated with several other disorders, including dermatitis herpetiformis, other autoimmune disorders and IgA deficiency.

Nutritional deficiencies, such as calcium and iron should be identified and treated. A gluten-free diet has been shown to quickly reverse GI symptoms and helps to avoid long-term complications, including enteropathy-associated T-cell lymphoma.[8] Dx

References
1. National Institutes of Health Consensus Development Conference Statement on Celiac Disease, June 28-30, 2004. Gastroenterology 2005; 128(4 Suppl 1):S1-9.
2. Dube C, Rostom A, Sy R, et al: The Prevalence of Celiac Disease in Average-Risk and At-Risk Western European Populations: A Systematic Review. Gastroenterology 2005; 128(4 Suppl 1):S57-67.
3. Wallace RA: Clinical Audit of Gastrointestinal Conditions Occurring Among Adults with Down Syndrome Attending a Specialist Clinic. J Intellect Dev Disabil 2007; 32(1):45-50.
4. Shan L, Molberg O, Parrot I, et al: Structural Basis for Gluten Intolerance in Celiac Sprue. Science 2002; 297(5590):2275-9.
5. Rostom A, Dube C, Cranney A, et al: The Diagnostic Accuracy of Serologic Tests for Celiac Disease: A Systematic Review. Gastroenterology 2005; 128(4 Suppl 1):S38-46.
6. Rostom A, Murray JA, Kagnoff MF: American Gastroenterological Association (AGA) Institute Technical Review on the Diagnosis and Management of Celiac Disease. Gastroenterology 2006; 131(6):1981-2002.
7. Janatuinen EK, Kemppainen TA, Julkunen RJ, et al: No Harm From Five Year Ingestion of Oats in Celiac Disease. Gut 2002; 50(3):332-5.
8. Holmes GK, Prior P, Lane MR, et al: Malignancy in Celiac Disease. Effect of a Gluten Free Diet. Gut 1989; 30(3):333-8.