Celiac Disease:

A Common Condition That Can Fool You

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Presented at the University of Calgary's CME Rounds, February 2007.

Until recently, celiac disease (CD) has flown under the radar for many FPs. Advances in diagnostics and disease awareness have led to earlier diagnosis and identification of persons at risk for developing CD. The apparent increase in the incidence of CD has led to more questions for practitioners who manage these patients.

Pathophysiology and epidemiology

CD is a disorder characterized by chronic, small intestinal inflammation in response to gluten found in wheat, rye and barley. The classic features on small bowel biopsy include villous atrophy and crypt hyperplasia which resolve with the introduction of a gluten-free diet (GFD). Recent studies have identified the specific 33 amino acid peptide in gluten that is responsible for triggering the immunological events of CD.[1] This small peptide crosses the epithelial barrier in the small intestine, interacts with antigen-presenting cells triggering immune activation and destruction of the epithelial cells that line the small bowel.

Several recent epidemiological studies have shown that CD is much more common than previously thought, with a prevalence rate of approximately 1% in Europe and North America.[2] Prevalence rates vary greatly depending on whether the study reports positive serology or positive histological changes on biopsy. Generally, CD is more common in Caucasian populations and is less common in

Meet Alice

Alice, 66, is a nurse with chronic iron deficiency anemia, presumably due to heavy menstrual periods, which she has experienced since adolescence.

She has also had 4 pregnancies, 1 of which was complicated by moderate postpartum hemorrhage.

There have been no clinical or biochemical features at any time to suggest malabsorption; in fact, she has a lifelong history of intermittent constipation. Iron supplementation has corrected her anemia, at times in the past, but her ferritin has never normalized.

Alice is seen by a hematologist, who feels that her anemia is likely due to menstrual and pregnancy-related blood loss.

Several months following a hysterectomy, she had persistent hypochromic, microcytic anemia, despite oral iron supplementation. At that time, a celiac disease (CD) screen was negative (normal IgA), but duodenal biopsies confirmed CD.

She had a complete response to a gluten-free diet (GFD). Subsequently, 2 of her children are found to have low ferritin, although preserved hemoglobin (Hgb). Neither child had any GI symptoms, but 1 had a positive CD serology. Both were found to have CD confirmed by duodenal biopsy.

For more info on Alice, turn to page 21...

Alice's case cont'd...

A GI specialist was asked to see Alice due to profound anemia. Her Hgb is 74 g/L (hypochromic, microcytic, low ferritin).

Alice is transfused 2 units of red cells due to profound weakness. She occasionally consumes nonsteroidal anti-inflammatory agents but denies abdominal pain or GI blood loss. She denies any GI symptoms other than occasional episodes of constipation.

She recalls that her mother had problems with anemia and she mentiones that 2 of her mother's children and 1 grandchild have had low iron levels.

Alice's endoscopy and colonoscopy, as well as small bowel follow-through, are normal. Biopsies from her duodenum reveal Marsh Type 1 CD. She is started on a GFD and is given a course of IV iron. Six months later, Alice's Hgb is 151 g/L with normal red cell indices. Repeat duodenal biopsies 8 months after starting a GFD were normal.

Discussion

This case highlights that CD can present without GI symptoms and that serological CD testing can be negative even in the setting of normal IgA levels. CD is suspected in Alice, as she has a normal colonoscopy, no further menstrual loss, no GI blood loss and she fails to respond to iron. The critical point is that we did not let her negative tissue transglutaminase antibody (with a normal IgA) sway us from performing duodenal biopsies and thus confirming the diagnosis.

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Asians and African Americans. Almost all (approximately 99%) individuals with CD express the major histocompatibility complex antigens HLA-DQ2 or HLA-DQ8. Thus, if a person is negative for HLA-DQ2 or DQ8 it is very unlikely that they have or will develop CD. HLA typing is extremely expensive and is not a helpful screening tool since HLA-DQ2 and DQ8 antigens can be present in up to 25% to 40% of the general population.[3]

Over time, the histological classification of CD has changed. Up until approximately 20 years ago, a positive CD biopsy was defined as flat duodenal/jejunal mucosa (villous atrophy and crypt hyperplasia). Now the Marsh criteria are used to define the histological changes of CD and they encompass much more subtle alterations that, in the past, would not have met the standard criteria for CD.

A Marsh I lesion is defined by an increase in the number of intraepithelial lymphocytes. Marsh II is characterized by crypt hyperplasia and Marsh III is villous atrophy and crypt hyperplasia. Thus, even 10 to 20 years ago, most centers did not recognize Marsh I and II lesions as CD and, as a result, these patients would not have been appropriately diagnosed.

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Presentation

In the past, CD was most readily recognized in its classic form in children suffering growth failure and severe GI symptoms. Now, atypical

presentations are common in which patients have few or no GI symptoms and testing for CD is prompted by such findings as:

- iron deficiency,
- osteoporosis, or
- infertility (Table 1).

Furthermore, individuals can have silent disease with no symptoms but only histologic changes of CD. With such a wide spectrum of presenting signs and symptoms, it is easy to appreciate how many cases may escape diagnosis. It is not uncommon that patients with mild CD symptoms are mistakenly given the diagnosis of irritable bowel syndrome.

Table 1
Atypical presentations of CD

- Iron or folate deficiency anemia
- Osteoporosis
- Infertility
- Abnormal liver enzymes
- Chronic constipation
- Arthralgias
- Anxiety/depression
- Dementia
- Polyneuropathy
- Ataxia
- Epilepsy
- Dental hypoplasia

Disease associations

Due to shared susceptibility genes, CD is associated with Type 1 diabetes mellitus and dermatitis herpetiformis. Other autoimmune disorders may coexist with CD (Table 2). IgA deficiency is more common among CD patients and the diagnostic implications of this are mentioned below. CD is also more common in individuals with Down syndrome.

Table 2
Conditions associated with CD

- Family history of CD
- Dermatitis herpetiformis (DH) (90%-95% of patients with DH have CD)
- Type 1 diabetes mellitus
- Autoimmune thyroid disease
- Addison's disease
- Down syndrome
- Lymphocytic colitis
- IgA deficiency
- Sjögren's syndrome

Complications

When matched to appropriate controls, there appears to be excess mortality in patients presenting with classic CD. Excess deaths are attributable to malignancy, most often intestinal and extraintestinal forms of non-Hodgkin's lymphoma (NHL). A GFD likely reduces the risk of NHL in these patients. Excess mortality is not apparent in patients with mild or asymptomatic CD, but there is a lack of comprehensive data in this regard.

Diagnosis

The complete clinical entity of CD is often referred to as an iceberg, with classic cases comprising the easily visible tip and the bulk of diagnoses remaining obscure. Therefore, the first step in the diagnosis is maintaining a strong awareness of that which lies beneath the water. In patients suspected of having CD, serological detection of either IgA tissue transglutaminase antibody (tTGA) or IgA antiendomysial antibody (EMA) are recommended

as initial screening tests.[4] In adults, both EMA and tTGA have a sensitivity of > 90% and a specificity of > 95% (defined in Marsh III patient populations).[4] However, the sensitivity of these tests is substantially reduced (in some cases by < 50%) in milder histological grades of CD (Marsh I and II, which can make up 10% to 30% of all celiac patients).[3] Selective IgA deficiency is present in 2% to 3% of patients with CD, so it is advisable to simultaneously measure serum IgA levels in patients undergoing CD screening to reduce the risk of false negative tTGA or EMA.[4]

Duodenal biopsy

Duodenal biopsy examination remains the gold standard for establishing the diagnosis and should be performed in all patients with a positive serologic test before committing them to a GFD. Furthermore, a negative celiac serology should not preclude duodenal biopsy examinations in those in whom suspicion of CD remains. 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 GFD, then gluten should be re-introduced for four weeks prior to biopsy. In patients with histologically-confirmed CD who improved on a GFD, a repeat biopsy is generally not necessary.

Clearly those with GI symptoms such as chronic diarrhea and weight loss, should be tested for CD. FPs should also consider CD in patients with other autoimmune conditions and those with disease states known to be associated CD. First-degree relatives of those with CD should also be screened.

Treatment

A GFD that excludes wheat, rye and barley should be adhered to for life. We recommend a consultation with a dietitian for those with newly-diagnosed CD. Recent studies suggest that oats are safe to ingest but oat products can be contaminated with gluten unless the company specifically states the product is gluten-free.[5] Although most will note improvement in their symptoms within six weeks of starting a GFD, there are some that take up to six months for symptoms to resolve. Those that fail to improve on a GFD should be assessed by a gastroenterologist.

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