

Celiac Disease-Casting the Net

Update and Current Controversies

Celiac disease (CD) is an immune-mediated inflammatory enteropathy occurring in genetically susceptible individuals who ingest seed storage proteins from wheat, rye, or barley. Symptoms improve on a gluten-free diet. Studies over the past several years demonstrate an increased prevalence of CD of approximately 0.5-1.5% in many populations in South and North America, Europe, North Africa, the Middle East, India, and Australia, while the disease is rare in the Far East, Sub-Saharan Africa, and possibly in Amerindians. Classic clinical manifestations involve the gastrointestinal tract, while atypical clinical features of CD may affect several extraintestinal sites. CD is associated with several genetic and autoimmune disorders and relatives of CD patients are also at increased risk of disease. Individuals who make HLA DQ2 or DQ8 molecules are at risk for CD. Our knowledge of CD has increased rapidly over the past several years, accompanied by a generation of questions and controversies, particularly regarding diagnosis-how wide should we cast the net for CD? Many institutions such as ours use endoscopy with multiple biopsies of the proximal small intestine obtained during visualization of the mucosa, while others continue to advocate capsule biopsy which provides a larger tissue specimen and may be less expensive than endoscopy, although the patient receives radiation. Similarly, some institutions orient intestinal biopsies prior to fixation, while at others including ours, orientation occurs during embedding. Current controversies regarding the histology of CD include the existence of patchy disease in the small intestine, choice of an optimal grading system, routine use of special stains, and significance of low-grade lesions. We and others have noted variable histologic changes in different parts of the small intestine and CD patients, with most consistent changes seen in the duodenal bulb, suggesting that disease may manifest first in this region; others have noted less histologic variation between biopsy sites. Our institution and many others use the Marsh grading system as modified by Oberhuber et al., which includes low-grade lesions with relatively low specificity for CD; an alternative grading scheme proposed by Drut et al. emphasizes architectural changes. Increased intraepithelial lymphocytes (IELs) are a hallmark feature of CD, but are nonspecific, occurring in numerous other entities including autoimmune disorders, tropical sprue, infection, and peptic duodenitis. Recently, different threshold values for normal IEL density in the duodenum (20-25 IELs / 100 enterocytes) vs the jejunum (40 IELs / 100 enterocytes) have been proposed. Also, the distribution of IELs along the villous may help distinguish CD cases, in which IELs have a more even density along the villous with increased density at the villous tips, compared with the normal "decrecendo" pattern. Some authors advocate routine immunohistochemical staining for T-cell markers such as CD3 and CD8, and proliferation markers (Ki-67). While a flat, inflamed small intestinal mucosa obviously suggests a diagnosis of CD, most investigators agree that increased IELs unaccompanied by architectural changes, while nonspecific, may also occur in CD. As histology is at best highly suggestive of CD, serologic testing plays an invaluable role in diagnosis. Available tests determine titers for antibodies to alpha-gliadin (AGA), the alcohol-soluble protein fraction from wheat, or for auto-antibodies such as anti-reticulin (ARA), anti-endomysial (EMA), and anti-tissue transglutaminase (TGA) antibodies. Currently, some kits for IgA-TGA offer excellent sensitivity and specificity for detection of CD in children, and have been recommended as the first-line test for pediatric CD, generally offering comparable or superior results and/or technical advantages over the other tests available. Exceptions include patients with chronic liver disease / increased total serum IgA or patients with IgA deficiency. Laboratories must determine optimal cut-off values for their diagnostic kits and patient population. Recent advances in serologic techniques have led to a variety of recommended diagnostic algorithms/pathways. With the improvement of serologic tests, some authors have suggested that biopsy may not be required as the "gold standard" for all new cases of CD, if TGA titers are high and the patient responds to a gluten-free diet. In contrast, patients with equivocal initial serologic and/or biopsy results may benefit from additional studies such as additional serologic tests or genetic testing. The potential to screen general populations for CD with genetic and serologic tests has received recent attention. In summary, CD is a relatively common disease in many parts of the world, including Latin America, and current variation in diagnostic practices suggests that different nets may be cast in different populations, with similar results, while studies continue to refine optimal criteria for diagnosis.

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