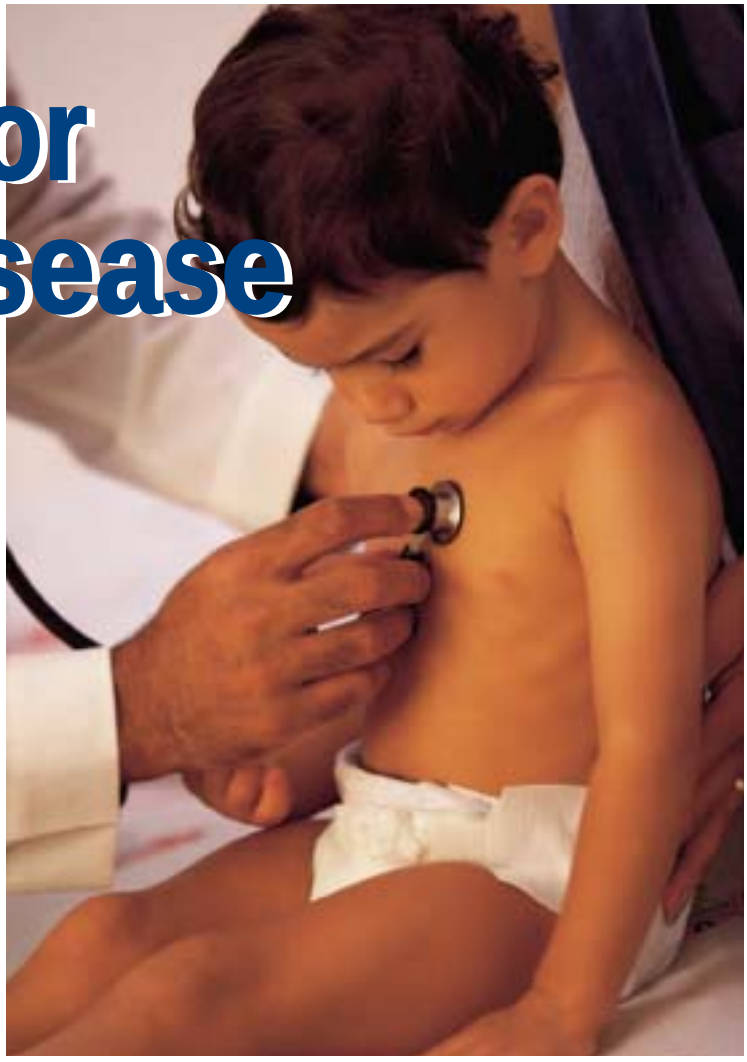
Looking for Celiac Disease in All the Wrong Places



By Bob Issenman, MD, FRCPC; and Rabin Persad, MD, FRCPC

The advent of serological tests has changed much of what we thought we knew about the prevalence and natural history of celiac disease, which has traditionally been thought of as a childhood condition. The classic picture of the typical celiac patient depicts a wasted child with long eyelashes, protuberant abdomen and wasted buttocks (Figures 1 to 3). These characteristics, however, are now seen infrequently in primary-care (Table 1). It is evident that celiac disease may be 10 to 20 times more common than previously thought and the age of diagnosis is rising dramatically.[1] This has important implications for primary-care physicians, as celiac disease may provide a diagnosis for patients with a variety of chronic unexplained symptoms.

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History of Celiac Disease

One hundred years ago, Dr. Samuel Gee described this malabsorption syndrome in children as the "celiac" or wasting condition. With the advent of the sweat chloride test, it was possible to determine that some of these children actually had cystic fibrosis. The specific diagnosis of celiac disease occurred with development of the peroral intestinal

biopsy in the 1960s. With the promulgation of upper gastrointestinal endoscopy, it became possible to routinely test patients for celiac disease. Intestinal mucosal specimens demonstrate classic pathological changes. A "flat gut" results from shortened microvilli and elongated crypts coupled with intense inflammatory changes. Increased intra-epithelial lymphocytes are recognized as a hallmark histologic finding.

Serologic Screening and Antigliadin Antibodies

The need for a simple clinical screening tool has been evident for many years. The antigliadin antibody test, developed in Europe, was never given much credence in North America. The antigliadin antibodies are raised in a number of other intestinal conditions, making this test complex and confusing when used outside of a specialized center.[2]

Antigliadin testing is based on an immunoglobulin (Ig)G or IgA antibody to the antigen present in dietary wheat. It is highly variable from laboratory to laboratory with a reported sensitivity of 52% to 100% and a specificity of 58% to 98%.[3] The IgG test is more sensitive than the IgA, but there are more false-positive results. The IgA may be falsely negative in the 10% of celiac patients with IgA deficiency — a known correlation (Table 2).

Antiendomysial antibody. The usefulness of serological testing leapt forward with the advent of tests for the presence of an antiendomysial (EMA) antibody. This antibody is directed against the "endomysium," the cell's skeletal structure, as demonstrated by immunoflourescence. The test has a sensitivity of 90% to 100%, with a specificity of up to 100%.[4] It remains unreliable in IgA deficiency (2.5% to 10% of celiacs), and, therefore, quantitative immunoglobulins should be performed to aid in interpreting the test. It has proven useful in academic health centers, but is not wide-

Summary

Looking for Celiac Disease in All the Wrong Places

- It is evident that celiac disease may be 10 to 20 times more common than previously thought and the age of diagnosis is rising dramatically.
- It has been traditionally taught that celiac disease occurs in approximately one in every 4,000 to 8,000 Caucasians, but was most prevalent in the Irish (one in 450). Subsequent population-based studies, using diagnosis by peroral biopsy, have indicated a prevalence as follows: Irish; one in 152; Italians with "dyspepsia," one in 103; Swedish (blood donors), one in 256; and Brazilians one in 680.
- Celiac disease is common in individuals with other autoimmune conditions. It occurs in 8% to 12% of Type 1 diabetics, patients with thyroiditis, or Sjorgen's syndrome.
- The most recent test developed for celiac disease is TTG or tissue transglutaminase antibody testing. This antibody is directed against an enzyme that catalyzes the cross-link formation between glutamine residues and lysine residues in substrate proteins.
- Intestinal biopsy is still recommended to confirm the diagnosis of celiac disease.
- Diet is the mainstay of treatment for celiac disease. The celiac patient must avoid all forms of gluten, a fraction of the gliadin protein, present in grains, such as wheat, barley, rye and trillicate.

ly available because of its high cost (up to $150 at commercial laboratories). There also are limitations on the availability of tissue substrate (*i.e.*, monkey esophagus or fetal umbilical tissue) and testing has a significant subjective variability. The availability of EMA, however, has allowed for population studies that suggest a much a higher prevalence of the disease.[5]

Serum tissue transglutaminase. The most recent test developed is tissue transglutaminase antibody testing (TTG).[6] This antibody is directed against an enzyme that catalyzes the cross-link formation between glutamine residues and lysine residues in substrate proteins. Some believe it to be the epitope in the autoimmune attack on the intestinal lining. This enzyme linked immunoabsorbent assay (ELISA) has a sensitivity of 61% to 98% and a specificity of 95% to 99%.[7] It will be widely available, relatively inexpensive and more reliable when used in decentralized laboratories.

Prevalence of Celiac Disease

It has been traditionally taught that celiac disease occurs in approximately one in every 4,000 to 8,000 Caucasians, but was most prevalent in the Irish (one in 450).[8] Subsequent population-based studies, using diagnosis by peroral biopsy, have indicated a prevalence of one in every 450 to 500 people in Ireland, Scotland and Switzerland.[5] A decrease in prevalence occurred transiently in European countries when changes in infant feeding practices were instituted. This resulted in a delayed introduction of wheat products in infancy.[9] Using serological screening, it is now apparent that celiac disease is much more common than initially thought. Studies have suggested a

Table 1

Signs of Classic Celiac Disease

- Undernutrition
- Long eyelashes
- Malaise/irritability
- Anorexia
- Vomiting/diarrhea/constipation
- Delayed gross motor development
- Decreased muscle mass
- Decreased subcutaneous tissue
- Protuberant abdomen
- Wasted buttocks

Table 2

Tests for Celiac Disease

	Sensitivity	Specificity
• Antigliadin antibody	42% to 100%	58% to 98%
• Antiendomysial antibody	90% to 100%	97% to 100%
• Tissue transglutaminase	61% to 98%	95% to 98%
• Small intestinal biopsy	The “Gold Standard”	

Table 3

Prevalence of Celiac Disease

Irish	1 in 152
Italians with "dyspepsia"	1 in 103
Swedish (blood donors)	1 in 256
Brazilians	1 in 680

prevalence of one in 152 Irish people, one in 256 Swedes (random blood donors), one in 680 Brazilians and one in 103 "dyspeptic" Italians (Table 3).[5]

Genetics and Autoimmune Conditions

Celiac disease is common in individuals with other autoimmune conditions. It occurs in 8% to 12% of Type 1 diabetics and patients with thyroiditis or Sjorgen's syndrome (Figure 3).[10,11] There is a known association with dermatitis herpetiformis, selective IgA deficiency and Down's syndrome (7%) (Figure 4).[12,13] There seems to be a genetic predisposition to celiac disease. Two per cent to 15% of first-degree relatives are affected, and there is a 70% concordance with monozygotic twins.[14,15] This is based on a strong association with human leukocyte antigen (HLA) class II antigen with DQ2 present in 95% of European celiacs (Table 4).[16]

The Rising Age of Diagnosis

The availability of serologic testing has changed our appreciation of celiac disease. With the use of serologic testing, the age at which patients are diagnosed with celiac disease has been steadily rising. This rise has been particularly evident in Sweden.[8] For unexplained reasons, celiac disease is far less clinically evident in older children and adult patients. This may be so because the nutrients needed to sustain growth are more critical during rapid growth in early childhood. By contrast, celiac disease most powerfully damages the proximal intestine. An older child or an adult may

Table 4

Conditions Associated with Celiac Disease

• Dermatitis herpitiformis	67% to 95%
• First-degree relative with celiac disease	2% to 15%
• Selective IgA deficiency	2% to 10%
• Unexplained cerebellar ataxia	16%
• Autoimmune thyroid disease	8%
• Diabetes	5% to 12%
• Down's syndrome	7%
• Recurrent abdominal pain (children)	1%
• Unexplained seizures	1%

Table 5

Celiac Disease Beyond Infancy

- Underweight
- Growth failure/short stature
- Delayed puberty
- Ammenorhea
- Infertility/chronic miscarriage
- Anemia
- Osteoporosis
- Chronic diarrhea
- Lactose/fructose intolerance
- Irritable bowel syndrome

be able to "recapture" nutrients in less damaged areas of the lower bowel and modify the effects of malnutrition. Chronic malnutrition, however, can more seriously affect a patient's health. Malabsorption can lead to iron deficiency anemia, vitamin D deficiency, which can result in rickets, vitamin A deficiency, which can cause night-blindness and vitamin K deficiency, which can lead to hemorrhagic manifestations. Meanwhile, peripheral neuropathy and cerebellar atrophy may result from Vitamin E deficiency.

Symptoms After Infancy

Once children are beyond the toddler years, growth failure may be less evident than chronic digestive complaints (Table 5). Celiac disease can cause chronic abdominal pain and diarrhea in otherwise healthy looking children. In some cases, the inflammatory changes cause anorexia leading to constipation. In other children, mucosal brush border damage results in malabsorption of lactose or fructose. These symptoms may improve with dietary modification, but suspicion of underlying celiac disease should remain in children who are intolerant to both sugars.

Nevertheless, many children are underweight or shorter than expected. Delayed development of secondary sexual characteristics can lead to amenorrhea in younger girls and infertility in young women. Other patients may conceive, but can experience habitual fetal loss. Symptoms of irritable bowel syndrome can result from celiac disease at any age. Chronic iron deficiency anemia refractory to oral iron results from undiagnosed celiac disease in 4% of adults with anemia.[17] Findings of premature osteoporosis or unexplained fractures also require investigation. Many patients with histologic disease may be asymptomatic or merely

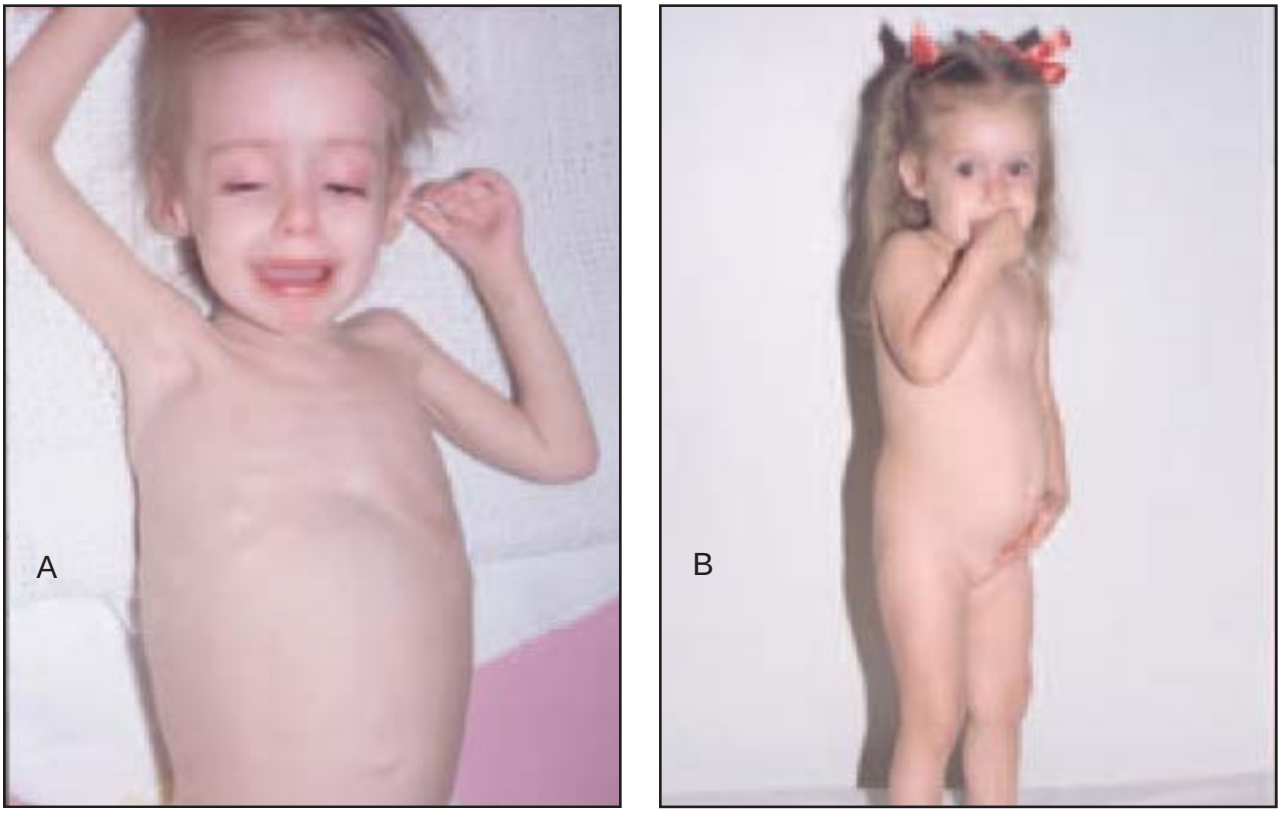

Figure 1. A child showing the clinical findings typical of celiac disease (1A = before; 1B = the same child after six months on a gluten-free diet).

experience unexplained fatigue. Patients diagnosed later in life appreciate the improvement they experience in chronic irritability when treated. It has been suggested that unexplained seizures associated with cerebellar calcification can be attributed to the condition.[18]

Treatment

Diet is the mainstay of treatment for celiac disease. The celiac patient must avoid all forms of gluten, a fraction of the gliadin protein, present in grains, such as wheat, barley, rye and trillicate. Gluten is literally the "glue," which contains carbon dioxide bubbles created by the fermentation of yeast when bread rises. It is the structural protein in most baked products in western culture. Wheat is omnipresent in sauces as a thickening agent and is used in food coatings of all varieties. There is some debate about whether oats should be included in a gluten-free diet. There may be minimal gluten in pure oat products, but the milling process and transport practices in ships lead to significant cross contamination.

It is estimated the substitutions required in the diet have increase food costs by 30%.[19] Furthermore, such diet restrictions require a unique lifestyle change that imposes a heavy social burden on the patient.

Figure 2. A young teenager with autoimmune hyperthyroid disorder. The risk of celiac disease is 8%.

Quiescent Celiac Disease

Many patients find that symptoms subside after switching to a gluten-free diet. This leads patients to believe they have outgrown their celiac disease. However, histologic damage continues in most of these patients, eroding the "intestinal reserve" required to fight infection or deal with other stresses, such as surgery, pregnancy or aging. Dr. Marku Maki argues celiac disease is the prototype automimmune disease — that celiac patients should remain gluten free to avoid priming of the immune system against other vulnerable tissues, such as thyroid and pancreatic beta cells.[5] This theory remains unproven.

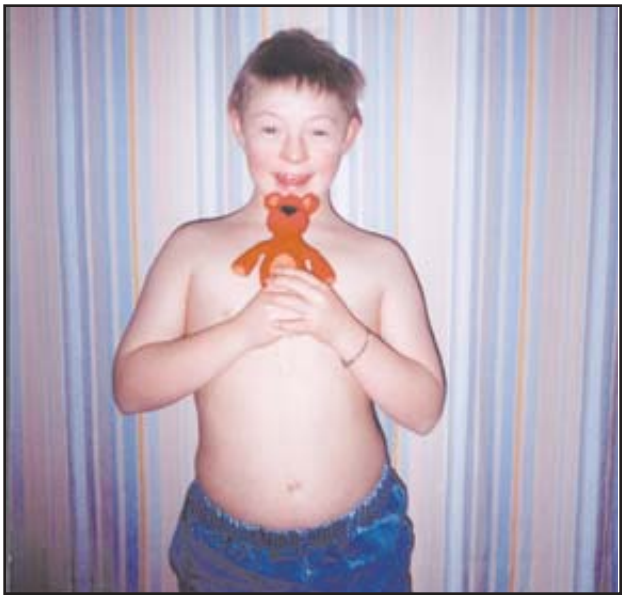

Figure 3. A child with two risk factors: Down's syndrome and diabetes, subsequently shown to have celiac disease.

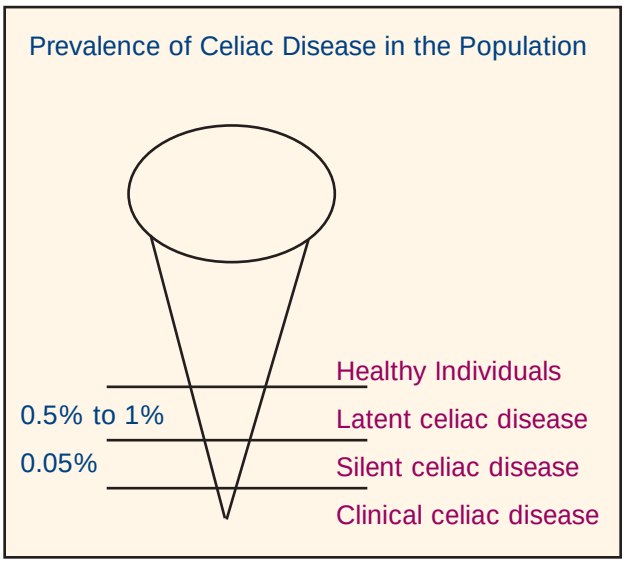

Figure 4. This diagram indicates the prevalence of diagnosed celiac disease as a small proportion of the total number of individuals with undiagnosed disease and those who will subsequently develop the flat gut bowel lesion.
Adapted from reference 5.

There appears to be an increased risk of small bowel lymphoma and adenocarcinoma in adults with celiac disease. It is anticipated that adherence to a gluten-free diet modifies this risk. There may be some patients who undergo a period of quiescent disease. It is imprudent, however, to rely on patients' symptoms and impractical to subject patients to repeated biopsies when making the diagnosis. It may be that the serologic tests will facilitate patient monitoring for compliance and relapse (Figure 4).

The Necessity of Intestinal Biopsy

Some patients question the necessity of biopsy diagnosis with the availability of highly specific and reliable blood tests. A diagnosis of celiac disease has classically required three intestinal biopsies:

- A biopsy on gluten;
- A biopsy off gluten; and
- A biopsy with "gluten challenge."

These guidelines have been modified to recommend one biopsy at diagnosis and a suitable clinical response to a gluten-free diet. Biopsy proponents argue that incontrovertible evidence is required to place an individual on a lifelong diet with significant economic, health and social implications.

Lastly, the sensitivity and specificity of serological testing has not yet been established when conducted in the primary-care setting, as opposed to a tertiary-care environment. As the debate has not been resolved, it seems prudent to continue to refer patients for expert evaluation. It is important that physicians and patients avoid the temptation of trying a gluten-free diet. Both blood tests and the "flat gut" appearance of the small intestinal mucosa required to confirm diagnosis revert to normal in an uncertain fashion on a gluten-free diet.

The Role of Dieticians and the Canadian Celiac Society.

The important role of expert nutritional counseling and peer support cannot be understated. The gluten-free diet is a difficult one. Tracking changes in food product manufacturing and labeling require the specialized expertise of registered dieticians and the coordinating role played by the Canadian Celiac Society. All newly diagnosed celiacs should be referred to a registered dietician and put in touch with the Canadian Celiac Society.

Summary

For years, celiac patients have complained their symptoms were routinely ignored or dismissed with minimal medical evaluation. The average adult with celiac disease has had symptoms for 10 years before diagnosis. With improvements in screening and diagnosis, it is clear the disease is far more common than previously appreciated. There are a myriad of symptoms that result from the primary disease or the resulting malabsorption. Accordingly, physicians need to adjust their understanding of the importance of this widespread disease. New serologic testing offers the prospect of better screening in high-risk groups and effective diagnosis and treatment for many more Canadians. When the true prevalence is known, it will undoubtably generate demand for wider availability of gluten-free products and changes in food regulation, labeling and processing. CME

References

1. Walker-Smith JA: Celiac Disease. In: Walker WA, Durie PR, Hamilton RJ, et al (eds.) P*ediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, Management.* Second Edition. Mosby, St. Louis, 1996, pp. 840-61.
2. Troncone R, Ferguson A: Anti-gliadin antibodies. JPGN, 1991; 12:150-8.
3. Chartrand LJ, Agulnik J, Vanounou T, et al: Effectiveness of antigliadin antibodies as a screening test for celiac disease in children. Can Med Assoc J 1997; 157:527-33.
4. Del Rosario M, Fitzgerald JF, Chong SK, et al: Further studies of anti-gliadin antibodies in patients with suspected celiac disease. Scand, J Gastro 1996; 31:61-7.
5. Maki M: Changing features of celiac disease. In: Lohenemi S, Collin P, Maki M (eds.) *Changing Features of Celiac Disease.* Tampere, Finland, 1998, pp.1-6.
6. Dietrich W, Ehnis T, Bauer M, et al: Identification of tissue transglutaminase as the autoantigen of celiac disease. Nat Med 1997; 3:797-801.
7. Dietrich W, Laag E, Schopper H, et al: Autoantibodies to tissue transglutaminase: As predictors of celiac disease. Gastroenterol 1998; 15:1317-21.
8. Davidson LSP, Fountain JR: Incidence of sprue syndrome with some observation on the natural history. Br Med J 1950; 1:1157-61.
9. Challacombe DN, Mescrow IK, Elliot K, et al: Changing infant feeding practices and declining incidence of coeliac disease in West Somerset. Arch Dis Child 1997; 77:206-9.
10. De Vitis I, Ghirlanda G, Gasbarrini G: Prevalence of coeliac disease in Type I diabetes: A multicentre study. Acta Pediatric 1996; 412(suppl):56-7.
11. Maclaurin BP, Matthews N, Kilpatrick JA: Coeliac disease associated with autoimmune thyroiditis, Sjogren's syndrome, and a lymphocytotoxin serum factor. Aust N Z J Med 1972; 4:405-11.
12. Fry L, Leonard JN, Swain AF, et al: Long-term follow-up of dermatitis herpetiformis with and without dietary gluten withdrawal. Br J Derm 1982; 107(6):631-40.
13. George EK, Mearin ML, Bougquant J, et al: Screening for celiac disease in Dutch children with associated diseases. Acta Pediatric 1996; 412(suppl):52-3.
14. Stenhammer L, Brandt A, Wagermark J: A family study of coeliac disease. Acta Pediatric Scand 1982; 71:625-8.
15. Trier JS: Celiac sprue. N Engl J Med 1991; 325(24):1709-19.
16. Sollid L, Thorsby E: HLA susceptibility genes in celiac disease: Genetic mapping and role in pathogenesis. Gastroenterol 1993; 105:910-22.
17. Jewell D, Godkin A: The pathogenesis of celiac disease. Gastroenterol 1998; 115:206-10.
18. Luostarinen LK, Collin PO, Peraahom J, et al: Celiac disease in patients with cerebellar ataxia of unknown origin. Ann Med 2001; 33(6):445-9.
19. McNeish AS, Harms K, Rey J, et al: Re-evaluation of diagnostic criteria for coeliac disease. Arch Dis Child 1979; 54:783-6.

Suggested Reading

1. Farrell RJ, Kelley CP: Current concepts: Celiac Sprue, New Engl J Med 2002; 346:180-8.
2. Fitzpatrick KP, Sherman PM, Ipp M, et al: Screening for celiac disease in children with recurrent abdominal pain. J Pediatr Gastroenterol Nutr 2001; 33:250-2.