Celiac sprue (the great modern-day imposter)

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Purpose of review

To review the current epidemiological information on celiac disease and the various presentations and associated.

Recent findings

Epidemiologic studies reveal celiac disease to be common, occurring in approx. 1% of the population. It is being diagnosed worldwide, even in developing countries. The classic mode of presentation has become less common, with diarrhea or a malabsorption syndrome as the mode of presentation in fewer than 50% of individuals. The other major modes of presentation are iron-deficiency anemia, osteoporosis, screening of family members, or incidentally at endoscopy done for dyspepsia or reflux. Neurological presentations may include peripheral neuropathy or ataxia. Arthritis is commonly found in patients with celiac disease when systematically sought. Patients often have a previous diagnosis of irritable bowel syndrome. Autoimmune diseases occur more frequently (three to ten times more) in those with celiac disease than the general population. However, this increased incidence of autoimmune diseases is not prevented by early diagnosis of celiac disease.

Summary

We will review the various associated diseases/presentations of celiac disease. The heterogeneity of the symptoms can make the diagnosis challenging and certainly the great modern-day imposter.

Keywords

celiac disease, endomysial antibody, gluten, intestinal biopsy, tissue transglutaminase antibody

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Abbreviation

HLA histocompatibility locus antigen

1040-8711

Introduction

Celiac disease is a gluten-sensitive enteropathy that occurs in genetically predisposed individuals and responds to the withdrawal of gluten from the diet. Those with dermatitis herpetiformis are considered to have celiac disease. Celiac disease was originally considered a rare malabsorption syndrome of childhood. However, it is now recognized as primarily an adult disease [1]. The development of the disease requires both genetic and environmental factors. The human major histocompatibility molecules DQ2 and DQ8 are essential genetic factors for the development of celiac disease, with the majority of patients carrying DQ2 alleles (DQA1*05/DQB1*02). In the remaining patients, an association with DQ8 (DQA1*0301/DQB1*0302) is found. These histocompatibility locus antigen (HLA) genes occur in up to 40% of the Caucasian population. They are considered to confer only 40% of the genetic risk to develop celiac disease; the rest is attributable to non-HLA genes that as yet have to be definitively identified [2]. Overall, 10% of first-degree relatives have celiac disease. This increases to 20% if there are affected sibling pairs in the family [3].

Environmental factors include a requirement for gluten ingestion. Gluten is the term for the storage proteins of wheat. The alcohol-soluble fraction of gluten, gliadin, is toxic in celiac disease, along with similar proteins in barley (hordeins) and rye (secalins). The role of other environmental factors is evident from the fact that only a small percentage of those ingesting wheat develop celiac disease. Lack of breastfeeding, a large amount of gluten in infant formula and gastrointestinal infections increase the risk of celiac disease in infancy [4–8]. In addition to protecting against the development of celiac disease, breastfeeding delays the onset and alters the clinical presentation of celiac disease in children [9–11]. The timing of the introduction of gluten is also important. For most, protection is afforded if gluten introduction occurs during the fourth and sixth months [12••].

Epidemiology

Screening studies have revealed that celiac disease is very common, approaching 1% of the population [13–16,17•]. It is recognized across the globe, including Asia [18], the Middle East [15,19], North Africa [20], and South America [21]. These high prevalence rates are based on serologic screening studies. The bulk of those with celiac disease are currently undiagnosed [13], although the rate of diagnosis is increasing. Murray *et al*. [1] noted a 10-fold increase in the prevalence of celiac disease in 2001

compared to 1950. The disease is considered to be underdiagnosed [22]. As a result, patients have a long duration of symptoms prior to diagnosis [23]. The delay in diagnosis has been attributed to physician delay rather than a delay in patients seeking health care [24].

Pathogenesis

Those with celiac disease develop an immunological reaction to a fragment of the gliadin molecule, a 33-amino acid peptide, that is resistant to digestion by gastric, pancreatic and duodenal enzymes [25]. The immune reaction in the lamina propria is triggered when gliadin is deamidated by tissue transglutaminase, an enzyme that is present in most tissues. The deamidated gliadin subsequently binds to either DQ2 or DQ8 molecules on antigen-presenting cells. An inflammatory process is then initiated by gliadin-restricted CD4+ T cells [26], resulting in villous injury. The characteristic intraepithelial lymphocytosis is considered to occur by a different mechanism, one involving the innate immune system [27]. Villous atrophy and intraepithelial lymphocytosis are the histologic hallmarks of the disease.

Diagnosis

While the small-bowel biopsy is the gold standard for the diagnosis of celiac disease, serologic tests are important in the determination of who should be referred for biopsy. The National Institutes of Health Consensus Development Conference on Celiac Disease was convened in June 2004 (the final statement is available online at http://consensus.nih.gov/PREVIOUSSTATEMENTS.htm#2004CeliacDisease) [22]. For that conference, Rostom *et al.* [28•] reviewed the literature on serologic testing for celiac disease. They recommended that the IgA anti-tissue transglutaminase or endomysial antibody be used for serologic testing. This is based on a sensitivity and specificity of >90%. In addition they considered the antigliadin antibodies to have too low a sensitivity and specificity to be of value in the diagnosis of celiac disease.

Selective IgA deficiency is 15-fold more common among those with celiac disease than the general population [29]. As a result, those with celiac disease and selective IgA deficiency will lack both IgA endomysial and tissue transglutaminase antibodies. In order to detect celiac disease in this population an IgG tissue transglutaminase antibody should be sought [30–32].

Clinical presentation

Celiac disease more resembles a multisystem disorder rather than a primary gastrointestinal disease. Over the last two decades the percentage of patients presenting with diarrhea and malabsorption syndrome has decreased. Instead the majority of patients present in atypical ways, with so-called silent celiac disease in which diarrhea is not prominent. Some patients are truly asymptomatic, detected by screening of at risk groups that include relatives of those with diagnosed celiac disease [16], type 1 diabetes [33,34] and Down syndrome [35,36]. A large screening study from England detected celiac disease in 1%; those with positive celiac serologies considered themselves well, although they had mild anemia and a reduction in bone density [37]. Other patients present as critically ill with a malabsorption syndrome or enteropathy-associated lymphoma. The reason for the tremendously varied presentation is unclear.

For those diagnosed with celiac disease the clinical presentation has changed; more patients with less severe symptoms are being diagnosed [1]. Lo *et al.* [38] also reviewed 227 patients with biopsy proven celiac disease. Diarrhea was the most common presenting symptom in 62% and the rest were silent. Among the patients in the silent group, 15% had anemia or osteoporosis, 13% were found through screening and 8% were found incidentally at endoscopy. Fewer patients in recent years were presenting with classic symptoms of diarrhea; 43% now compared with 73% before 1993 [38].

Less dramatic presentations include irritable bowel syndrome. One study revealed that a significant portion (5%) of patients were misdiagnosed with irritable bowel syndrome [39]. In another study, 30% of those diagnosed with celiac disease had a previous diagnosis of irritable bowel syndrome [23]. Clinicians need to be aware that celiac disease does not always present with diarrhea and the various presentations need to be recognized. We will discuss various associated diseases/presentations.

Hematological presentations

Oxentenko *et al.* [40] found a high incidence of celiac disease – 15% – among patients undergoing endoscopy for evaluation of iron-deficiency anemia. The same authors detected celiac disease among 8.7% of 103 patients subjected to routine duodenal biopsy at endoscopy for iron-eficiency anemia [41]. Karnam *et al.* [42] found a lower incidence of celiac disease – 2.8% – in their prospective study of iron-deficient patients who underwent both endoscopy and colonoscopy. They concluded that all patients with iron deficiency should have duodenal biopsies routinely as celiac disease is a common etiology that is treatable [42]. Five percent of another series of iron-deficiency anemic patients had celiac disease; all those with celiac disease had been refractory to oral iron therapy [43].

Anemia was present in 90% of children with celiac disease in an Indian series [44]. Hematologic manifestations among 22 children with celiac disease included anemia alone in 19 (86.3%), leukopenia in two (9%) patients, and thrombocytopenia in one (4.5%) patient. Twelve patients

had an iron-deficiency anemia that coexisted with zinc and vitamin B_{12} deficiency [45]. Despite iron supplementation and a gluten-free diet, abnormal hematologic parameters may persist [46]. Vitamin B_{12} deficiency was formerly considered rare in celiac disease. However, recent studies reveal that it is common, occurring in 12 and 40% of two recent case series [47,48].

Osteoporosis

Reduced bone density is common in patients with celiac disease [49]. A few studies have shown that screening osteoporotic patients with celiac antibodies is beneficial in diagnosing patients with silent celiac disease [50]. The prevalence of celiac disease has been found in 2–7% patients with osteoporosis. Worsening T scores have also been found to correlate with more severe celiac disease [49,51]. Among 431 patients presenting for bone-density determination, the prevalence of celiac disease was 1.2% for patients with osteopenia, and 2.1% for those with osteoporosis [52]. The yield of screening postmenopausal patients with osteoporosis for celiac disease is low and not considered worthwhile [53].

Rheumatologic presentations

Among the extraintestinal manifestations of celiac disease, arthritis is common. There have been many case reports of arthritis being the presenting symptom in both adults and children [54–60]. In one study, systematic examination of patients with celiac disease revealed arthritis to be common; arthritis was present in 26% of 200 celiac patients compared with 7.5% controls. They also found a higher incidence of arthritis among untreated celiac patients. The arthritis was seronegative and oligoarticular, similar to the other enteroarthritides [61]. Bone scintigraphy was carried out to detect early acute inflammatory lesions in 22 adult celiac patients and was positive for sacroiliitis in 14 cases (63.6%) [62]. However, a study in which a cohort of 160 patients with rheumatoid arthritis were screened for celiac disease failed to reveal an increased prevalence of celiac disease [63]. Increased prevalence of celiac disease in juvenile chronic arthritis is controversial [64,65].

False-positive tissue transglutaminase antibodies have also been found in patients with arthritis [66], and IgA tissue transglutaminase antibodies have also been detected in joint fluid of arthritic patients who do not have celiac disease [67].

Luft *et al.* [68] tested sera of patients with various rheumatologic disorders including Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis for the presence of tissue transglutaminase antibodies and found an increased incidence of celiac disease only among patients with Sjogren's syndrome, of 10%. They did not find an increased frequency of celiac disease among the others [68]. Similarly, Rensch *et al.* [69] screened patients with systemic lupus erythematosus for antigliadin and antiendomysial antibodies. They found no patients with endomysial antibodies. They did find 23% patients to have positive antigliadin antibodies but no evidence of celiac disease [69].

Neurologic presentations

Neurologic symptoms as a presenting feature have become increasingly recognized. The most well-documented associations are with peripheral neuropathies, ataxia and epilepsy. The celiac neuropathy is typically a sensory, small-fiber neuropathy. A recent study reported that 23% of patients with celiac disease who were well controlled by diet had peripheral neuropathy compared with a 4% occurrence rate in the control group [70]. At a tertiary-care referral center, celiac neuropathy was found in 2.5% of the patients evaluated for neuropathy [71]. Furthermore, celiac disease was found in 5% of patients with symptoms of neuropathy *and* normal electrodiagnostic studies, making celiac disease an important diagnostic consideration in the evaluation of 'small-fiber' or idiopathic sensory neuropathies [71].

Ataxia is one of the more frequent neurologic syndromes associated with celiac disease [72,73] and is often not suspected due to a lack of gastrointestinal symptoms or signs of malabsorption. The frequency of biopsy-confirmed celiac disease in patients with ataxia of unknown origin ranges from 12 to 15% [73,74]. One series, however, found no celiac disease-associated antibodies in 32 patients with idiopathic cerebellar ataxia [75]. Celiac disease-associated ataxia often lacks particular clinical features that would distinguish it from other forms of cerebellar ataxia [76]. Severe ataxia in association with celiac disease may respond to intravenous gammaglobulin [77].

Epilepsy is more recognized as an association with childhood celiac disease than adult celiac disease [78–80]. Two large studies of adults with celiac disease failed to detect an increased association [81,82]. The syndrome of occipital calcification, epilepsy in patients with celiac disease, may be reversed with a gluten-free diet [83–85].

Blood-test abnormalities

Various blood-test abnormalities have been associated with celiac disease. The more common ones include hyperamylasemia, abnormal liver-function tests, and hypocholesterolemia. Elevated serum amylase, due to macroamylasemia, has been found more commonly among untreated celiac patients than those on a gluten-free diet [86]. In the cases of recurrent pancreatitis, abnormalities of cholecystokinin, impaired secretin release, and papillary stenosis have been proposed [87].

Abnormal liver tests have been frequently associated with celiac disease. In particular, hypertransaminasemia may be present in up to 40% of patients, both adults and children, and is usually reversible with a gluten-free diet [88–91]. Celiac disease is detected as the cause of about 10% of cases of cryptogenic hypertransaminasemia [92,93]. The exact etiology of the liver abnormalities is unknown. Biopsies have shown nonspecific hepatitis as well as steatosis.

It is not a surprising finding that patients with celiac disease often have low cholesterol. Ciacci *et al.* [94] reviewed 100 patients with hypochromic anemia who did not have diarrhea and found an inverse correlation between cholesterol level and prevalence of celiac disease. All patients with celiac disease were found to have cholesterol values below 156 mg/100 ml. They suggested that among patients with hypochromic anemia, high or high–normal cholesterol could possibly be used to exclude celiac disease [94]. Lower low-density lipoprotein levels have been found in patients with celiac disease and these levels did not necessarily rise after a gluten-free diet [95].

Oral and facial manifestations

Celiac disease may be manifested in the mouth by the Sjogren's syndrome, [96,97], recurrent apthous stomatitis [98–101] and dental enamel defects [102–105]. Recently a large forehead has been proposed as a sign of celiac disease [106•]. This is due to failure of growth of the visceral cranium after weaning, and as a result the middle third of the face is proportionally smaller than the forehead.

Autoimmune diseases

Autoimmune diseases occur in those with celiac disease three to ten times more frequently than in the general population [107–109]. These diseases (Table 1) include thyroid disease [108,110,111], autoimmune hepatitis and cholangitis [112–114], primary biliary cirrhosis [115], type 1 diabetes mellitus [116], Sjogren's syndrome [96], Addison's disease [117], peripheral neuropathy, psoriasis [118] and cardiomyopathy [119].

Table 1 Diseases associated with celiac disease

Category	Disease
Neurologic	Peripheral neuropathy [71,121–125], cerebellar ataxia [126–128], epilepsy [76], migraines [129]
Endocrine	Type 1 diabetes mellitus [130–132], autoimmune thyroid disorders [133], Addison's disease [117], alopecia areata [134]
Cardiac	Idiopathic dilated cardiomyopathy [135], autoimmune myocarditis [120]
Hepatic	Primary biliary cirrhosis [136], autoimmune hepatitis [137,138], autoimmune cholangitis [139]
Other	Anemia [140], osteoporosis [141], Turner syndrome [142], Down syndrome [143], dental enamel defects [144], sarcoidosis [145], recurrent acute pancreatitis [87]
Rheumatologic	Oligoarticular arthritis [61], juvenile arthritis [65], Sjogren's syndrome [96]

This association with other autoimmune diseases is thought to be secondary to shared HLA alleles, a common immunologic mechanism and the presence of celiac disease itself. Duration of gluten exposure was suggested by Ventura *et al.* [109] to be linked to the development of autoimmune diseases. However, two recent studies have refuted this [107,108]. There are reports of improvement of various autoimmune diseases in patients with celiac disease on a gluten-free diet. These include the neuropathy [71], cardiomyopathy [120] and thyroid disease [108]. However, most associated autoimmune diseases do not improve after a gluten-free diet and diagnosis of celiac disease does not protect from the development of the associated autoimmune diseases [107,108].

Conclusion

There are a host of diseases associated with celiac disease (Table 1). The varied clinical presentations make the diagnosis challenging. It is therefore important for clinicians of all subspecialities to be aware of the varied symptoms/diseases associated with celiac disease and consider performing celiac serologies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 127).

1 Murray JA, Van Dyke C, Plevak MF, *et al.* Trends in the identification and clinical features of celiac disease in a North American community, 1950–2001. Clin Gastroenterol Hepatol 2003; 1:19–27.

2 Louka AS, Sollid LM. HLA in coeliac disease: unravelling the complex genetics of a complex disorder. Tissue Antigens 2003; 61:105–117.

3 Book L, Zone JJ, Neuhausen SL. Prevalence of celiac disease among relatives of sib pairs with celiac disease in U.S. families. Am J Gastroenterol 2003; 98:377–381.

4 Hernell O, Ivarsson A, Persson LA. Coeliac disease: effect of early feeding on the incidence of the disease. Early Hum Dev 2001; 65 Suppl:S153–S160.

5 Ivarsson A, Persson LA, Hernell O. Does breast-feeding affect the risk for coeliac disease? Adv Exp Med Biol 2000; 478:139–149.

6 Ivarsson A, Hernell O, Stenlund H, Persson LA. Breast-feeding protects against celiac disease. Am J Clin Nutr 2002; 75:914–921.

7 Ivarsson A, Hernell O, Nystrom L, Persson LA. Children born in the summer have increased risk for coeliac disease. J Epidemiol Community Health 2003; 57:36–39.

8 Ivarsson A, Persson LA, Nystrom L, *et al.* Epidemic of coeliac disease in Swedish children. Acta Paediatr 2000; 89:165–171.

9 Persson LA, Ivarsson A, Hernell O. Breast-feeding protects against celiac disease in childhood – epidemiological evidence. Adv Exp Med Biol 2002; 503:115–123.

10 Maki M, Kallonen K, Lahdeaho ML, Visakorpi JK. Changing pattern of childhood coeliac disease in Finland. Acta Paediatr Scand 1988; 77: 408–412.

11 D'Amico MA, Holmes J, Stavropoulos SN, *et al.* Presentation of pediatric celiac disease in the United States: prominent effect of breastfeeding. Clin Pediatr (Phila) 2005; 44:249–258.

12 •• Norris JM, Barriga K, Hoffenberg EJ, *et al.* Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. JAMA 2005; 293:2343–2351.
This paper provides insight into the mechanism of celiac disease autoimmunity and forms part of the basis of advising mothers to introduce solids containing gluten between 4 and 6 months of age if the child is at risk from developing celiac disease.

13 West J, Logan RF, Hill PG, *et al.* Seroprevalence, correlates, and characteristics of undetected coeliac disease in England. Gut 2003; 52:960–965.

14 Maki M, Mustalahti K, Kokkonen J, *et al.* Prevalence of Celiac disease among children in Finland. N Engl J Med 2003; 348:2517–2524.

15 Tatar G, Elsurer R, Simsek H, *et al.* Screening of tissue transglutaminase antibody in healthy blood donors for celiac disease screening in the Turkish population. Dig Dis Sci 2004; 49:1479–1484.

16 Fasano A, Berti I, Gerarduzzi T, *et al.* Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. Arch Intern Med 2003; 163:286–292.

17 • Bingley PJ, Williams AJ, Norcross AJ, *et al.* Undiagnosed coeliac disease at age seven: population based prospective birth cohort study. Br Med J 2004; 328:322–323.
A population-based study showing a 1% prevalence of celiac disease.

18 Sood A, Midha V, Sood N, Malhotra V. Adult celiac disease in northern India. Indian J Gastroenterol 2003; 22:124–126.

19 Shahbazkhani B, Malekzadeh R, Sotoudeh M, *et al.* High prevalence of coeliac disease in apparently healthy Iranian blood donors. Eur J Gastroenterol Hepatol 2003; 15:475–478.

20 Catassi C, Ratsch IM, Gandolfi L, *et al.* Why is coeliac disease endemic in the people of the Sahara? Lancet 1999; 354:647–648.

21 Gomez JC, Selvaggio GS, Viola M, *et al.* Prevalence of celiac disease in Argentina: screening of an adult population in the La Plata area. Am J Gastroenterol 2001; 96:2700–2704.

22 National Institutes of Health. Statement. NIH Consensus Development Conference on Celiac Disease, 2004. http://consensus.nih.gov/PREVIOUS-STATEMENTS.htm#2004CeliacDisease. [Accessed 25 October 2005]

23 Green PHR, Stavropoulos SN, Panagi SG, *et al.* Characteristics of adult celiac disease in the USA: results of a national survey. Am J Gastroenterol 2001; 96:126–131.

24 Lankisch PG, Martinez Schramm A, Petersen F, *et al.* Diagnostic intervals for recognizing celiac disease. Z Gastroenterol 1996; 34:473–477.

25 Shan L, Molberg O, Parrot I, *et al.* Structural basis for gluten intolerance in celiac sprue. Science 2002; 297:2275–2279.

26 Alaedini A, Green PH. Narrative review: celiac disease: understanding a complex autoimmune disorder. Ann Intern Med 2005; 142:289–298.

27 Meresse B, Chen Z, Ciszewski C, *et al.* Coordinated induction by IL15 of a TCR-independent NKG2D signaling pathway converts CTL into lymphokine-activated killer cells in celiac disease. Immunity 2004; 21: 357–366.

28 • Rostom A, Dube C, Cranney A, *et al.* The diagnostic accuracy of serologic tests for celiac disease: a systematic review. Gastroenterology 2005; 128:S38–S46.
A systematic review of the literature commissioned by the National Institutes of Health.

29 Collin P, Maki M, Keyrilainen O, *et al.* Selective IgA deficiency and coeliac disease. Scand J Gastroenterol 1992; 27:367–371.

30 Lenhardt A, Plebani A, Marchetti F, *et al.* Role of human-tissue transglutaminase IgG and anti-gliadin IgG antibodies in the diagnosis of coeliac disease in patients with selective immunoglobulin A deficiency. Dig Liver Dis 2004; 36:730–734.

31 Korponay-Szabo IR, Laurila K, Szondy Z, *et al.* Missing endomysial and reticulin binding of coeliac antibodies in transglutaminase 2 knockout tissues. Gut 2003; 52:199–204.

32 Dahlbom I, Olsson M, Forooz NK, *et al.* Immunoglobulin G (IgG) anti-tissue transglutaminase antibodies used as markers for IgA-deficient celiac disease patients. Clin Diagn Lab Immunol 2005; 12:254–258.

33 Bouguerra R, Ben Salem L, Chaabouni H, *et al.* Celiac disease in adult patients with type 1 diabetes mellitus in Tunisia. Diabetes Metab 2005; 31:83–86.

34 Aktay AN, Lee PC, Kumar V, *et al.* The prevalence and clinical characteristics of celiac disease in juvenile diabetes in Wisconsin. J Pediatr Gastroenterol Nutr 2001; 33:462–465.

35 Cogulu O, Ozkinay F, Gunduz C, *et al.* Celiac disease in children with Down syndrome: importance of follow-up and serologic screening. Pediatr Int 2003; 45:395–399.

36 Mackey J, Treem WR, Worley G, *et al.* Frequency of celiac disease in individuals with Down syndrome in the United States. Clin Pediatr (Phila) 2001; 40:249–252.

37 West J, Logan RF, Card TR, *et al.* Fracture risk in people with celiac disease: a population-based cohort study. Gastroenterology 2003; 125:429–436.

38 Lo W, Sano K, Lebwohl B, *et al.* Changing presentation of adult celiac disease. Dig Dis Sci 2003; 48:395–398.

39 Sanders DS, Carter MJ, Hurlstone DP, *et al.* Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. Lancet 2001; 358: 1504–1508.

40 Oxentenko AS, Grisolano SW, Murray JA, *et al.* The insensitivity of endoscopic markers in celiac disease. Am J Gastroenterol 2002; 97:933–938.

41 Grisolano SW, Oxentenko AS, Murray JA, *et al.* The usefulness of routine small bowel biopsies in evaluation of iron deficiency anemia. J Clin Gastroenterol 2004; 38:756–760.

42 Karnam US, Felder LR, Raskin JB. Prevalence of occult celiac disease in patients with iron-deficiency anemia: a prospective study. South Med J 2004; 97:30–34.

43 Hershko C, Hoffbrand AV, Keret D, *et al.* Role of autoimmune gastritis. Helicobacter pylori and celiac disease in refractory or unexplained iron deficiency anemia. Haematologica 2005; 90:585–595.

44 Mohindra S, Yachha SK, Srivastava A, *et al.* Coeliac disease in Indian children: assessment of clinical, nutritional and pathologic characteristics. J Health Popul Nutr 2001; 19:204–208.

45 Fisgin T, Yarali N, Duru F, *et al.* Hematologic manifestation of childhood celiac disease. Acta Haematol 2004; 111:211–214.

46 Kapur G, Patwari AK, Narayan S, Anand VK. Iron supplementation in children with celiac disease. Indian J Pediatr 2003; 70:955–958.

47 Dahele A, Ghosh S. Vitamin B12 deficiency in untreated celiac disease. Am J Gastroenterol 2001; 96:745–750.

48 Dickey W. Low serum vitamin B12 is common in coeliac disease and is not due to autoimmune gastritis. Eur J Gastroenterol Hepatol 2002; 14:425–427.

49 Meyer D, Stavropolous S, Diamond B, *et al.* Osteoporosis in a North American adult population with celiac disease. Am J Gastroenterol 2001; 96:112–119.

50 Nuti R, Martini G, Valenti R, *et al.* Prevalence of undiagnosed coeliac syndrome in osteoporotic women. J Intern Med 2001; 250:361–366.

51 Stenson WF, Newberry R, Lorenz R, *et al.* Increased prevalence of celiac disease and need for routine screening among patients with osteoporosis. Arch Intern Med 2005; 165:393–399.

52 Sanders DS, Patel D, Khan FB, *et al.* Case-finding for adult celiac disease in patients with reduced bone mineral density. Dig Dis Sci 2005; 50:587–592.

53 Gonzalez D, Sugai E, Gomez JC, *et al.* Is it necessary to screen for celiac disease in postmenopausal osteoporotic women? Calcif Tissue Int 2002; 24:24.

54 Bourne JT, Kumar P, Huskisson EC, *et al.* Arthritis and coeliac disease. Ann Rheum Dis 1985; 44:592–598.

55 Collin P, Korpela M, Hallstrom O, *et al.* Rheumatic complaints as a presenting symptom in patients with coeliac disease. Scand J Rheumatol 1992; 21:20–23.

56 Chakravarty K, Scott DG. Oligoarthritis–a presenting feature of occult coeliac disease. Br J Rheumatol 1992; 31:349–350.

57 Bagnato GF, Quattrocchi E, Gulli S, *et al.* Unusual polyarthritis as a unique clinical manifestation of coeliac disease. Rheumatol Int 2000; 20:29–30.

58 Slot O, Locht H. Arthritis as presenting symptom in silent adult coeliac disease. Two cases and review of the literature. Scand J Rheumatol 2000; 29:260–263.

59 Evron E, Abarbanel JM, Branski D, Sthoeger ZM. Polymyositis, arthritis, and proteinuria in a patient with adult celiac disease. J Rheumatol 1996; 23:782–783.

60 Falcini F, Ferrari R, Simonini G, *et al.* Recurrent monoarthritis in an 11-year-old boy with occult coeliac disease. Successful and stable remission after gluten-free diet. Clin Exp Rheumatol 1999; 17:509–511.

61 Lubrano E, Ciacci C, Ames PR, *et al.* The arthritis of coeliac disease: prevalence and pattern in 200 adult patients. Br J Rheumatol 1996; 35:1314–1318.

62 Usai P, Bassotti G, Usai Satta P, *et al.* Oesophageal motility in adult coeliac disease. Neurogastroenterol Motil 1995; 7:239–244.

63 Francis J, Carty JE, Scott BB. The prevalence of coeliac disease in rheumatoid arthritis. Eur J Gastroenterol Hepatol 2002; 14:1355–1356.

64 George EK, Hertzberger-ten Cate R, van Suijlekom-Smit LW, *et al.* Juvenile chronic arthritis and coeliac disease in The Netherlands. Clin Exp Rheumatol 1996; 14:571–575.

65 Lepore L, Martelossi S, Pennesi M, *et al.* Prevalence of celiac disease in patients with juvenile chronic arthritis. J Pediatr 1996; 129:311–313.

66 Riente L, Chimenti D, Pratesi F, *et al.* Antibodies to tissue transglutaminase and Saccharomyces cerevisiae in ankylosing spondylitis and psoriatic arthritis. J Rheumatol 2004; 31:920–924.

67 Spadaro A, Sorgi ML, Scrivo R, *et al.* Anti-tissue transglutaminase antibodies in inflammatory and degenerative arthropathies [in Italian]. Reumatismo 2002; 54:344–350.

68 Luft LM, Barr SG, Martin LO, *et al.* Autoantibodies to tissue transglutaminase in Sjogren's syndrome and related rheumatic diseases. J Rheumatol 2003; 30:2613–2619.

69 Rensch MJ, Szyjkowski R, Shaffer RT, *et al.* The prevalence of celiac disease autoantibodies in patients with systemic lupus erythematosus. Am J Gastroenterol 2001; 96:1113–1115.

70 Luostarinen L, Himanen SL, Luostarinen M, *et al.* Neuromuscular and sensory disturbances in patients with well treated coeliac disease. J Neurol Neurosurg Psychiatry 2003; 74:490–494.

71 Chin RL, Sander HW, Brannagan TH, *et al.* Celiac neuropathy. Neurology 2003; 60:1581–1585.

72 0Hadjivassiliou M, Grunewald RA, Chattopadhyay AK, *et al.* Clinical, radiological, neurophysiological, and neuropathological characteristics of gluten ataxia. Lancet 1998; 352:1582–1585.

73 Pellecchia MT, Scala R, Filla A, *et al.* Idiopathic cerebellar ataxia associated with celiac disease: lack of distinctive neurological features. J Neurol Neurosurg Psychiatry 1999; 66:32–35.

74 Abele M, Burk K, Schols L, *et al.* The aetiology of sporadic adult-onset ataxia. Brain 2002; 125:961–968.

75 Combarros O, Infante J, Lopez-Hoyos M, *et al.* Celiac disease and idiopathic cerebellar ataxia. Neurology 2000; 54:2346.

76 Luostarinen L, Dastidar P, Collin P, *et al.* Association between coeliac disease, epilepsy and brain atrophy. Eur Neurol 2001; 46:187–191.

77 Sander HW, Magda P, Chin RL, *et al.* Cerebellar ataxia and coeliac disease. Lancet 2003; 362:1548.

78 Labate A, Gambardella A, Messina D, *et al.* Silent celiac disease in patients with childhood localization-related epilepsies. Epilepsia 2001; 42:1153–1155.

79 Arroyo HA, De Rosa S, Ruggieri V, *et al.* Epilepsy, occipital calcifications, and oligosymptomatic celiac disease in childhood. J Child Neurol 2002; 17: 800–806.

80 Pratesi R, Modelli IC, Martins RC, *et al.* Celiac disease and epilepsy: favorable outcome in a child with difficult to control seizures. Acta Neurol Scand 2003; 108:290–293.

81 Tengah DS, Holmes GK, Wills AJ. The prevalence of epilepsy in patients with celiac disease. Epilepsia 2004; 45:1291–1293.

82 Ranua J, Luoma K, Auvinen A, *et al.* Celiac disease-related antibodies in an epilepsy cohort and matched reference population. Epilepsy Behav 2005; 6:388–392.

83 Molteni N, Bardella MT, Baldassarri AR, Bianchi PA. Celiac disease associated with epilepsy and intracranial calcifications: report of two patients. Am J Gastroenterol 1988; 83:992–994.

84 Gobbi G, Bouquet F, Greco L, *et al.* Coeliac disease, epilepsy, and cerebral calcifications. The Italian Working Group on Coeliac Disease and Epilepsy. Lancet 1992; 340:439–443.

85 Gobbi G, Ambrosetto P, Zaniboni MG, *et al.* Celiac disease, posterior cerebral calcifications and epilepsy. Brain Dev 1992; 14:23–29.

86 Rabsztyn A, Green PH, Berti I, *et al.* Macroamylasemia in patients with celiac disease. Am J Gastroenterol 2001; 96:1096–1100.

87 Patel RS, Johlin FC Jr, Murray JA. Celiac disease and recurrent pancreatitis. Gastrointest Endosc 1999; 50:823–827.

88 Bardella MT, Fraquelli M, Quatrini M, *et al.* Prevalence of hypertransaminasemia in adult celiac patients and effect of gluten-free diet. Hepatology 1995; 22:833–836.

89 Dickey W, McMillan SA, Collins JS, *et al.* Liver abnormalities associated with celiac sprue. How common are they, what is their significance, and what do we do about them? J Clin Gastroenterol 1995; 20:290–292.

90 Novacek G, Miehsler W, Wrba F, *et al.* Prevalence and clinical importance of hypertransaminasaemia in coeliac disease. Eur J Gastroenterol Hepatol 1999; 11:283–288.

91 Farre C, Esteve M, Curcoy A, *et al.* Hypertransaminasemia in pediatric celiac disease patients and its prevalence as a diagnostic clue. Am J Gastroenterol 2002; 97:3176–3181.

92 Volta U, De Franceschi L, Lari F, *et al.* Coeliac disease hidden by cryptogenic hypertransaminasaemia. Lancet 1998; 352:26–29.

93 Bardella MT, Marino R, Meroni PL. Celiac disease during interferon treatment. Ann Intern Med 1999; 131:157–158.

94 Ciacci C, Cirillo M, Giorgetti G, *et al.* Low plasma cholesterol: a correlate of nondiagnosed celiac disease in adults with hypochromic anemia. Am J Gastroenterol 1999; 94:1888–1891.

95 Vuoristo M, Kesaniemi YA, Gylling H, Miettinen TA. Metabolism of cholesterol and apolipoprotein B in celiac disease. Metabolism 1993; 42:1386–1391.

96 Iltanen S, Collin P, Korpela M, *et al.* Celiac disease and markers of celiac disease latency in patients with primary Sjogren's syndrome. Am J Gastroenterol 1999; 94:1042–1046.

97 Patinen P, Aine L, Collin P, *et al.* Oral findings in coeliac disease and Sjogren's syndrome. Oral Dis 2004; 10:330–334.

98 Lahteenoja H, Toivanen A, Viander M, *et al.* Oral mucosal changes in coeliac patients on a gluten-free diet. Eur J Oral Sci 1998; 106:899–906.

99 Sedghizadeh PP, Shuler CF, Allen CM, *et al.* Celiac disease and recurrent aphthous stomatitis: A report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002; 94:474–478.

100 Aydemir S, Tekin NS, Aktunc E, *et al.* Celiac disease in patients having recurrent aphthous stomatitis. Turk J Gastroenterol 2004; 15:192–195.

101 Pastore L, De Benedittis M, Petruzzi M, *et al.* Importance of oral signs in the diagnosis of atypical forms of celiac disease [in Italian]. Recenti Prog Med 2004; 95:482–490.

102 Aine L, Maki M, Collin P, Keyrilainen O. Dental enamel defects in celiac disease. J Oral Pathol Med 1990; 19:241–245.

103 Aine L. Permanent tooth dental enamel defects leading to the diagnosis of coeliac disease. Br Dent J 1994; 177:253–254.

104 Maki M, Aine L, Lipsanen V, Koskimies S. Dental enamel defects in first-degree relatives of coeliac disease patients. Lancet 1991; 337:763–764.

105 Aine L, Maki M, Reunala T. Coeliac-type dental enamel defects in patients with dermatitis herpetiformis. Acta Derm Venereol 1992; 72:25–27.

106 • Finizio M, Quaremba G, Mazzacca G, Ciacci C. Large forehead: a novel sign of undiagnosed coeliac disease. Dig Liver Dis 2005; 37:659–664.
A unique paper suggesting a new sign for celiac disease: the large forehead!

107 Viljamaa M, Kaukinen K, Huhtala H, *et al.* Coeliac disease, autoimmune diseases and gluten exposure. Scand J Gastroenterol 2005; 40:437–443.

108 Sategna Guidetti C, Solerio E, Scaglione N, *et al.* Duration of gluten exposure in adult coeliac disease does not correlate with the risk for autoimmune disorders. Gut 2001; 49:502–505.

109 Ventura A, Magazzu G, Greco L. Duration of exposure to gluten and risk for autoimmune disorders in patients with celiac disease. SIGEP Study Group for Autoimmune Disorders in Celiac Disease. Gastroenterology 1999; 117:297–303.

110 Jiskra J, Limanova Z, Vanickova Z, Kocna P. IgA and IgG antigliadin, IgA anti-tissue transglutaminase and antiendomysial antibodies in patients with autoimmune thyroid diseases and their relationship to thyroidal replacement therapy. Physiol Res 2003; 52:79–88.

111 Ansaldi N, Palmas T, Corrias A, *et al.* Autoimmune thyroid disease and celiac disease in children. J Pediatr Gastroenterol Nutr 2003; 37:63–66.

112 Lawson A, West J, Aithal GP, Logan RF. Autoimmune cholestatic liver disease in people with coeliac disease: a population-based study of their association. Aliment Pharmacol Ther 2005; 21:401–405.

113 Volta U, Rodrigo L, Granito A, *et al.* Celiac disease in autoimmune cholestatic liver disorders. Am J Gastroenterol 2002; 97:2609–2613.

114 Sedlack RE, Smyrk TC, Czaja AJ, Talwalkar JA. Celiac disease-associated autoimmune cholangitis. Am J Gastroenterol 2002; 97:3196–3198.

115 Dickey W, McMillan SA, Callender ME. High prevalence of celiac sprue among patients with primary biliary cirrhosis. J Clin Gastroenterol 1997; 25:328–329.

116 Talal AH, Murray JA, Goeken JA, Sivitz WI. Celiac disease in an adult population with insulin-dependent diabetes mellitus: use of endomysial antibody testing. Am J Gastroenterol 1997; 92:1280–1284.

117 O'Leary C, Walsh CH, Wieneke P, *et al.* Coeliac disease and autoimmune Addison's disease: a clinical pitfall. Q J Med 2002; 95:79–82.

118 Ojetti V, Aguilar Sanchez J, Guerriero C, *et al.* High prevalence of celiac disease in psoriasis. Am J Gastroenterol 2003; 98:2574–2575.

119 Fonager K, Sorensen HT, Norgard B, Thulstrup AM. Cardiomyopathy in Danish patients with coeliac disease. Lancet 1999; 354:1561.

120 Frustaci A, Cuoco L, Chimenti C, *et al.* Celiac disease associated with autoimmune myocarditis. Circulation 2002; 105:2611–2618.

121 Simonati A, Battistella PA, Guariso G, *et al.* Coeliac disease associated with peripheral neuropathy in a child: a case report. Neuropediatrics 1998; 29:155–158.

122 Polizzi A, Finocchiaro M, Parano E, *et al.* Recurrent peripheral neuropathy in a girl with celiac disease. J Neurol Neurosurg Psychiatry 2000; 68:104–105.

123 Kaplan JG, Pack D, Horoupian D, *et al.* Distal axonopathy associated with chronic gluten enteropathy: a treatable disorder. Neurology 1988; 38: 642–645.

124 Chin RL, Latov N. Peripheral neuropathy and celiac disease. Curr Treat Options Neurol 2005; 7:43–48.

125 Alaedini A, Green PH, Sander HW, *et al.* Ganglioside reactive antibodies in the neuropathy associated with celiac disease. J Neuroimmunol 2002; 127:145–148.

126 Hadjivassiliou M, Grunewald RA, Davies-Jones GA. Idiopathic cerebellar ataxia associated with celiac disease: lack of distinctive neurological features. J Neurol Neurosurg Psychiatry 1999; 67:257.

127 Bushara KO, Goebel SU, Shill H, *et al.* Gluten sensitivity in sporadic and hereditary cerebellar ataxia. Ann Neurol 2001; 49:540–543.

128 Shill HA, Alaedini A, Latov N, Hallett M. Anti-ganglioside antibodies in idiopathic and hereditary cerebellar degeneration. Neurology 2003; 60:1672–1673.

129 Gabrielli M, Cremonini F, Fiore G, *et al.* Association between migraine and celiac disease: results from a preliminary case-control and therapeutic study. Am J Gastroenterol 2003; 98:625–629.

130 Lampasona V, Bonfanti R, Bazzigaluppi E, *et al.* Antibodies to tissue transglutaminase C in type I diabetes. Diabetologia 1999; 42:1195–1198.

131 Collin P, Kaukinen K, Valimaki M, Salmi J. Endocrinological disorders and celiac disease. Endocr Rev 2002; 23:464–483.

132 Bao F, Yu L, Babu S, *et al.* One third of HLA DQ2 homozygous patients with type 1 diabetes express celiac disease-associated transglutaminase autoantibodies. J Autoimmun 1999; 13:143–148.

133 Mainardi E, Montanelli A, Dotti M, *et al.* Thyroid-related autoantibodies and celiac disease: a role for a gluten-free diet? J Clin Gastroenterol 2002; 35:245–248.

134 Corazza GR, Andreani ML, Venturo N, *et al.* Celiac disease and alopecia areata: report of a new association. Gastroenterology 1995; 109:1333–1337.

135 Curione M, Barbato M, De Biase L, *et al.* Prevalence of coeliac disease in idiopathic dilated cardiomyopathy. Lancet 1999; 354:222–223.

136 Gillett HR, Cauch-Dudek K, Jenny E, *et al.* Prevalence of IgA antibodies to endomysium and tissue transglutaminase in primary biliary cirrhosis. Can J Gastroenterol 2000; 14:672–675.

137 Volta U, De Franceschi L, Molinaro N, *et al.* Frequency and significance of anti-gliadin and anti-endomysial antibodies in autoimmune hepatitis. Dig Dis Sci 1998; 43:2190–2195.

138 Sjoberg K, Lindgren S, Eriksson S. Frequent occurrence of non-specific gliadin antibodies in chronic liver disease. Endomysial but not gliadin antibodies predict coeliac disease in patients with chronic liver disease. Scand J Gastroenterol 1997; 32:1162–1167.

139 Davison S. Coeliac disease and liver dysfunction. Arch Dis Child 2002; 87:293–296.

140 Ransford RA, Hayes M, Palmer M, Hall MJ. A controlled, prospective screening study of celiac disease presenting as iron deficiency anemia. J Clin Gastroenterol 2002; 35:228–233.

141 Kemppainen T, Kroger H, Janatuinen E, *et al.* Osteoporosis in adult patients with celiac disease. Bone 1999; 24:249–255.

142 Bonamico M, Pasquino AM, Mariani P, *et al.* Prevalence and clinical picture of celiac disease in turner syndrome. J Clin Endocrinol Metab 2002; 87:5495–5498.

143 Agardh D, Nilsson A, Carlsson A, *et al.* Tissue transglutaminase autoantibodies and human leucocyte antigen in Down's syndrome patients with coeliac disease. Acta Paediatr 2002; 91:34–38.

144 Ventura A, Martelossi S. Dental enamel defects and coeliac disease. Arch Dis Child 1997; 77:91.

145 Rutherford RM, Brutsche MH, Kearns M, *et al.* Prevalence of coeliac disease in patients with sarcoidosis. Eur J Gastroenterol Hepatol 2004; 16:911–915.