

Clinical relevance of villous atrophy

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Introduction

Nutrient-induced injuries to the small intestine include coeliac disease, cow's milk protein enteropathy, soybean enteropathy, chicken-induced enteropathy and other food-sensitive enteropathies. Coeliac disease remains the dominant nutrient-induced enteropathy. The interaction of genetic, dietary and environmental factors is crucial to our understanding of the pathogenesis of this condition. Coeliac disease is a disease of the small intestine characterised by the development of villous atrophy in response to ingestion of dietary proteins contained in wheat, barley, and rye. Villous atrophy in turn results in malabsorption of essential nutrients with the development of steatorrhoea, weight loss and specific deficiency syndromes. Pathophysiology of gluten enteropathy is widely accepted as secondary to immunological mechanisms primarily related to T cell-mediated events. Coeliac disease is tightly linked genetically to genes encoded in the major histocompatibility complex (MHC) type, with a particular Class II allele (HLA-DQ) found in almost all patients. The most serious potential complication from longstanding CD is malignancy. The risk of developing a small intestinal lymphoma is increased only in patients on a reduced gluten or normal diet, and the role of a gluten-free diet in protecting against other malignancies has also been suggested. A strict gluten-free diet has become the cornerstone of the management of CD patients

and must be recommended for life in both, symptomatic and asymptomatic individuals.

Definition

Coeliac disease (CD) is now recognised to be an immunologically mediated enteropathy of the small intestine, characterised by lifelong intolerance to the gliadin and related prolamines from wheat and other cereals, that occurs in genetically predisposed individuals. Symptoms result from structural damage to the mucosa of the small intestine, which causes malabsorption. Normal mucosal architecture is restored after gluten-free diet; villous atrophy reappears when gluten is reintroduced into the diet (gluten challenge). After years of gluten exclusion, relapse of intestinal lesions recurs with gluten challenge (1, 2). It is the certainty of eventual relapse that differentiates CD from other childhood enteropathies and suggests that there is some additional property of the gluten molecules that affects enterocyte function or mucosal antigen presentation.

The concept that coeliac disease is permanent has been questioned not only by the observation of long periods of unexplained clinical remission after gluten reintroduction (3), but also by reports of cases who, after having shown a clear histological relapse and left on a normal gluten-containing diet, have subsequently shown a partial or total recovery of the histological lesion (4).

Therefore, although paediatric gastroenterologists all agree regarding the need for an initial biopsy, there is debate about whether three biopsies are necessary (5, 6).

Clinical features

It is now clear that CD can appear with different clinical manifestations. A better knowledge of CD has permitted the identification, not only of the classic forms of the disease characterised by gastrointestinal symptoms, but the identification of atypical forms, characterised by the absence of diarrhoea and the presence, sometimes, of symptoms not referring to a gastrointestinal pathology (Table 1).

In general, the first symptoms appear in the months following the introduction of gluten in the diet. The earlier that gluten is introduced into the diet, the shorter the interval between introduction and occurrence of the first symptoms. The first symptoms of CD, therefore, occur traditionally between 6 months and 2 years of age.

Table 1. Clinical presentation according to the age of onset of symptoms in PD

Symptoms	Signs
Classic presentation	
Chronic diarrhoea	Abdominal distention
Anorexia	Buttock wasting
Abdominal distention	Malnutrition/growth failure
Weight loss	Pallor
Vomiting	Irritability
Irritability/lethargy	Psychomotor delay
	Haematomas
	Rickets
Presentation at older age	
Asymptomatic	Glossitis, aphthous ulcers
Absence of diarrhoea	Short stature
Decreased appetite	Iron deficiency anaemia
Anorexia	Osteopaenia
Growth failure	Bruising
Pubertal delay	Arthritis/arthralgia
Menstrual irregularities	Enamel hypoplasia
Abnormal (loose) stools	Cerebral calcifications
Arthritis/arthralgia	
Abdominal pain	
Constipation	
Presentation at adulthood	
Anxiety/depression	Glossitis, aphthous ulcers
Chronic diarrhoea	Malnutrition
Anorexia	Spontaneous haemorrhage
Abdominal pain	Peripheral oedema
Infertility	Isolated megaloblastic anaemia
Paraesthesia	Cramps/tetany
Nocturnal diuresis	Digital clubbing
Bone pain	Proximal myopathy
Cerebrospinal degeneration	Peripheral neuropathy
	Variety of rashes
	Hipospilenism

In a minority of children, diagnosis is not made by the age of 5 years. CD can therefore be diagnosed at any time up to adulthood (7), because symptoms have been either ignored or misinterpreted (e.g. short stature), or because the disease is truly symptomless.

Classic presentation

There is considerable variation in the age of onset of symptoms in children with CD.

The characteristic features of the disease are most often encountered in infants 9–18 months of age. Within weeks or months of gluten introduction, the classical syndrome of chronic diarrhoea, failure to thrive or loss of weight, vomiting (especially before 9 months) and abdominal distension occurs. The stools are softer, paler, looser, bulkier, more frequent and offensive than usual, but seldom grossly greasy. Stools may be liquid, and dehydration may result during exacerbation of the disease. Oedemas, hypocalcaemia, anaemia and haematomas are characteristic in coeliac crisis. In contrast, stools are normal or even constipated in up to 15% of cases. Anorexia is common and may precede digestive symptoms; it may be prominent and hence wrongly attributed to psychological troubles.

On physical examination, the child is severely impaired. He or she is pale, looks miserable, and is depressed or irritable. Psychomotor development does not progress. Weight gain is more affected than height; subcutaneous fat disappears. Muscle wasting, affecting mostly the buttocks, thighs and shoulders, contrast markedly with the prominent abdominal distention.

Presentation at older age

Diagnosis of CD may be made in later childhood. Decreased appetite and abnormal stools are often revealed only on direct questioning. Constipation is more frequent at this stage than in infants. Dental enamel hypoplasia can be found in the permanent teeth as well as cerebral calcifications, epilepsy and other neurological disorders (8, 9). In early school years, apparently isolated short stature is a frequent presentation. A mild degree of abdominal distention, microcytic anaemia or osteoporosis may lead the diagnosis.

CD has been implicated in more than 15% of cases of children with retarded growth. In these children, plasma growth hormone measurements are low or normal, whereas the levels of insulin-like growth factor (IGF1) activity are reduced (10, 11), and can be returned to normal with the exclusion of gluten from the diet (11). On the other hand, the somatostatin concentration in the

jejunal mucosa of untreated patients in an active phase of the disease was significantly elevated, compared with controls and with those patients who had excluded gluten from their diets (12).

Asymptomatic and atypical presentations

CD may be symptomless and discovered only because of a systematic search through family studies, or in children affected with conditions associated with CD (Table 2). Today there is a vast amount of literature describing new, unexpected extraintestinal symptoms, or complications of CD.

Atypical symptoms such as arthritis, arthralgia, or isolated megaloblastic anaemia due to folic acid deficiency, have been reported (8), as well as isolated symptomatology such as short stature, abdominal pain, muscular hypotony, oedema, bleeding, epilepsy, ataxia, etc. without any other manifestations.

Low-grade enteropathy in coeliac disease

Recently, new concepts have emerged that have substantially changed our knowledge of coeliac disease, and questioned its very definition. It is now widely accepted that the term coeliac disease must not be limited to patients with severe enteropathy, although subtotal villous atrophy is still considered by many the hallmark of the disease (13). In fact, the gluten-dependent enteropathy may also be mild; only epithelial infiltration may be present, and with increasing severity of the histological picture, accompanied by crypt hyperplasia; sometimes the lesion is patchy.

The presence of immunohistochemical markers peculiar to coeliac disease, such as the increased density of epithelial $\gamma\delta$ + T cells, may be of help in identifying the gluten as the cause of these mild forms of enteropathy.

Latent coeliac disease

It also has become widely accepted that coeliac subjects may present with a severe or mild

enteropathy at different times of their life. There are subjects who had a normal jejunal biopsy while taking a normal diet and, at some other time, before or since, have had a flat jejunal biopsy which recovers on a gluten-free diet. For such subjects the definition of latent coeliac disease has been proposed (14–17). This definition can also be applied to “late relapsers” (3, 16, 18).

References

1. MEUWISSE GW. Diagnostic criteria in coeliac disease. *Acta Paediatr Scand* 1970; 59: 461–3.
2. MCNEISH AS, HARMS K, REY J, SHMERLING DH, WALKER-SMITH JA. Re-evaluation of diagnostic criteria for coeliac disease. *Arch Dis Child* 1979; 103: 783–6.
3. POLANCO I, LARRAURI J. Does transient gluten intolerance exist? In: KUMAR PJ, WALKER-SMITH JA, eds. *Coeliac disease: one hundred years*. Middlesex: Leeds University Press, 1990: 226–30.
4. SCHMITZ J, ARNAUD-BATTANDIER F, JOS J, REY J. Long-term follow-up of childhood coeliac disease. Is there a natural recovery? *Pediatr Res* 1984; 18: 1054.
5. WALKER-SMITH JA, GUANDALINI S, SCHMITZ J, SHMERLING DH, VISAKORPI JK. Revised criteria for the diagnosis of coeliac disease. Report of working group of ESPGAN. *Arch Dis Child* 1990; 65: 909–11.
6. POLANCO I, MEARIN ML, KRASILNIKOFF PA. The diagnosis of coeliac disease: one, two or three biopsies? *Pediatrics* 1996; 16: 350–7.
7. POLANCO I, BIEMOND I, VAN LEEUWEN A, et al. Gluten-sensitive enteropathy in Spain: genetic and environmental factors. In: MCCONNELL RB, ed. *The genetics of coeliac disease*. Lancaster: MTP Press, 1981: 211–34.
8. MÄKI M, KALLONEN K, LAHDEAHO ML, VISAKORPI JK. Changing pattern of childhood coeliac disease in Finland. *Acta Paediatr Scand* 1988; 77: 408–12.
9. GOBBI G, ANDERMANN F, NACCARATO S, BANCHINI G, eds. *Epilepsy and other neurological disorders in coeliac disease*. London: John Libbey, 1997.
10. SCHMITZ J. Coeliac disease in childhood. In: MARSH MN, ed. *Coeliac disease*. Oxford: Blackwell Scientific Publications, 1992: 17–48.
11. HERNÁNDEZ M, ARGENTE J, NAVARRO A, et al. Growth in malnutrition related to gastrointestinal diseases: coeliac disease. *Horm Res* 1992; 38 (suppl 1): 79–84.
12. ARILLA E, HERNÁNDEZ M, POLANCO I, ROCA B, PRIETO JC, VÁZQUEZ C. Molfication of somatostatin content and binding in jejunum from coeliac children. *J Pediatr Gastroenterol Nutr* 1987; 6: 228–33.
13. FERGUSON A, KINGSTONE K, GILLET H. Is biopsy the sole diagnostic criterion? In: MAKI M, COLLIN P, VISAKORPI JK, eds. *Coeliac disease*. Tampere: Coeliac Disease Study Group, 1997: 189–93.
14. POLANCO I, LARRAURI J, PRIETO G, GUERRERO J, PEÑA AS, VÁZQUEZ C. Severe villous atrophy appearing at different ages in two coelias siblings with identical HLA haplotypes. *Acta Paediatr Belg* 1980; 33: 276.
15. MÄKI M, Holm H, Koskimies S, Visakorpi JK. Latent coeliac disease. In: MEARIN ML, MULDER CJJ, eds. *Coeliac disease*. Dordrecht: Kluwer Academic Publishers, 1991: 153–6.
16. POLANCO I. Continuing need for three biopsies in

Table 2. Some conditions associated with CD

Dermatitis herpetiformis	Down's syndrome
Diabetes mellitus Type I	Selective IgA deficiency
Autoimmune thyroiditis	Rheumatoid arthritis
Hypogammaglobulinaemia	Vasculitis
Chronic active hepatitis	Primary biliar cirrhosis
Fibrosing alveolitis	Sjogren's syndrome
Crohn's disease	Ulcerative colitis
System lupus erithematosus	Cow's milk enteropathy
Glomerulonephritis	

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- children. In: MAKKI M, COLLIN P, VISAKORPI JK, eds. Coeliac disease. Tampere: Coeliac Disease Study Group, 1997: 171–6.
17. POLANCO I, MEARIN ML, LARRAURI J, BIEMOND I, WIPKINK-BAKKER A, PEÑA AS. The effect of gluten supplementation in healthy siblings of children with coeliac disease. *Gastroenterology* 1987; 92: 678–81.
18. POLANCO I, ed. Enfermedad celiaca. In: Actualidades en gastroenterología y hepatología, vol 20. Barcelona: JR Prous, 1996.