Coeliac disease

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Coeliac disease, or gluten sensitive enteropathy, is a common small bowel enteropathy resulting from ingestion of gluten in genetically susceptible individuals. Dermatitis herpetiformis (DH) is a related condition characterised by an itchy, blistering rash affecting knees, elbows, buttocks and back, with deposition of granular immunoglobulin (Ig) A at the dermoepidermal junction, including areas of the skin unaffected by blistering. Most patients have a small intestinal enteropathy: both this and the DH improve with exclusion of gluten.

Epidemiology

Coeliac disease is most prevalent in Europeans, although the disease has been reported in most races that eat wheat. There is a slight excess of affected women. A conservative estimate of prevalence in the UK is 1 in 1,200 although the lifetime risk could be as high as 1 in 300. Reports about changes in the incidence of this disorder are conflicting, and include the suggestion in the early 1980s that the rates were falling in the UK and Ireland. More recent studies from Sweden[1] and Sicily[2] have suggested a rise in both classical and later onset disease. The reasons for the difference in incidence between these populations remain largely unexplained. Duration of breast feeding and quantity of gluten consumed were found not to be significant when siblings of patients with coeliac disease were screened for the disorder[3]. However, these and other factors, such as viral exposure, may affect the severity of symptoms and age of presentation[4]. There is little doubt that coeliac disease will remain underdiagnosed unless high risk individuals are screened for the disorder[5,6].

Mortality rates for untreated coeliac disease are high. The risk of developing any gastrointestinal tumour (including oral and oesophageal tumours) is 10-fold higher than that of the general population and 40-fold higher for intestinal lymphoma. These rates return to normal after five years on a gluten free diet[7], and are the main reason for keeping to a gluten free diet even for patients who report few symptoms on reintroduction of gluten.

Key Points

- Coeliac disease is a common disorder, with increased morbidity and mortality in those who are not treated
- Prevalence is raised in autoimmune disorders, insulin-dependent diabetes, Down's syndrome and first-degree relatives of affected individuals
- Symptoms are variable and delay in diagnosis is frequent
- Anti-gliadin and anti-endomysial antibody titres are informative, but a small intestinal biopsy is essential to confirm the diagnosis
- Treatment by gluten free diet, avoiding wheat, rye, barley and probably oats, is effective

Genetics

Family studies confirm a significant genetic contribution to the risk of developing coeliac disease[8,9]:

- first-degree relatives, 10–20%
- HLA identical siblings, 30%
- monozygotic twins, approaching 100%.

Coeliac disease is strongly associated with the HLA DR3DQ2, HLA DR5/DR7 heterozygotes, and DR4DQ8[10]. The association is primarily through DQ rather than DR alleles and supports a central role for the DQ class II molecule in the pathogenesis of coeliac disease[11]. HLA associations account for 30% of the genetic risk of coeliac disease; segregation analyses suggest that at least one other, non-HLA linked, gene is required. Genome screening for these remaining susceptibility alleles is being undertaken, but the first reports of linkage in a small population have yet to be confirmed[12].

Cereal chemistry

Wheat is separated by milling into the outer husk (bran), the germ (semolina), and the white flour (endosperm) which constitutes about 72% of the grain by weight. Endosperm proteins include globulins, albumins and glutens (gliadins and glutenins), but only gliadin is toxic (see Fig 1). The exact structure of the toxic component of gliadin remains unknown but most toxicity resides in the α subfraction[13].

Pathogenesis

Coeliac disease affects the small intestine, with the severity of the lesion decreasing distally as the gluten is hydrolysed and becomes less toxic. The classical changes are mucosal atrophy, ranging from mild blunting

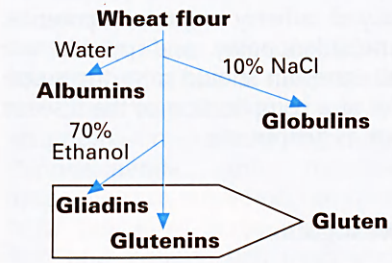


Figure 1. Osborne classification of wheat protein.

to total absence of the villi, and crypt hyperplasia reducing the normal ratio of villous height to crypt depth from between 3:1 and 5:1 to 1:1 or 1:2 (Figs 2, 3). The cell migration time from crypt to villous tip is reduced from 3–5 days to 1–2 days, and mitotic activity is seen closer to the crypt surface. The number of intra-epithelial lymphocytes is increased and there is marked infiltration of the lamina propria with plasma cells, supporting the immune hypothesis for coeliac disease[14].The proposed pathogenic mechanism is illustrated in Fig 4. Further evidence for an immune mechanism is supported by the heightened risk of developing a T cell lymphoma in gluten sensitive individuals who continue to be exposed to wheat.

An increased incidence of coeliac disease is found in patients with certain other conditions. The disease associations listed in Table 1 are partly explained by the known HLA associations, but there may be other shared environmental or genetic factors.

Table 1. Diseases associated with increased incidence of coeliac disease

- dermatitis herpetiformis
- trisomy 21 (Down's syndrome)
- insulin-dependent diabetes
- autoimmune thyroid disease
- inflammatory bowel disease
- chronic active hepatitis
- other autoimmune diseases

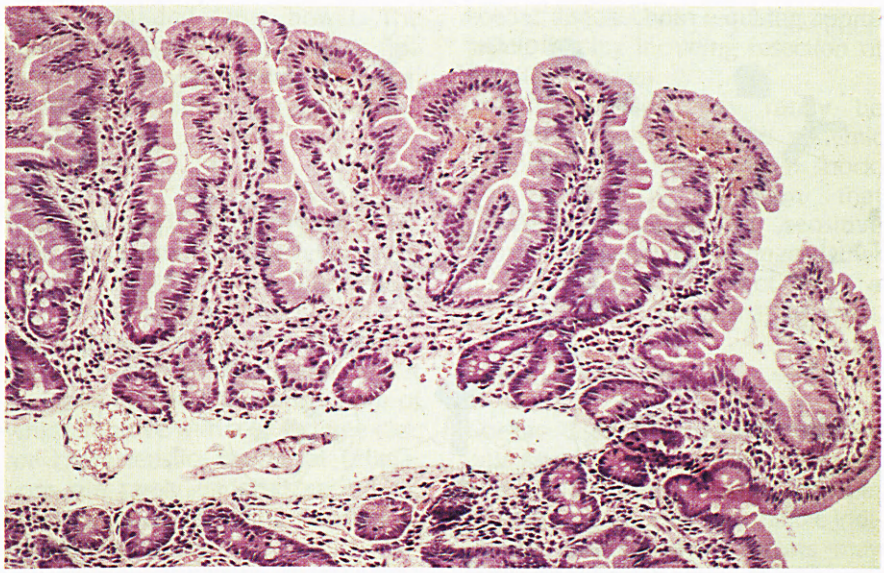


Figure 2. Normal jejunal mucosa.

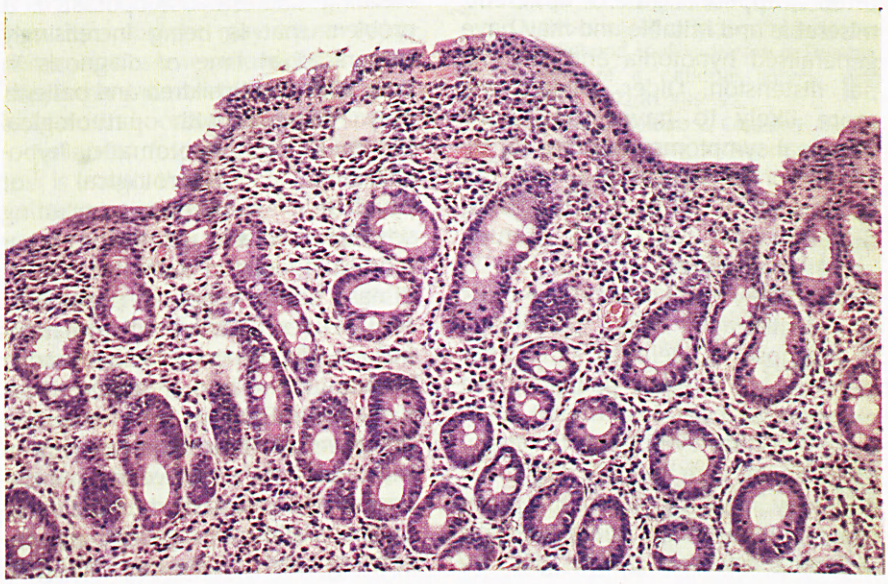
Clinical features

Signs and symptoms

Symptoms at presentation range from asymptomatic individuals, usually adults, diagnosed through screening programmes to children with classical coeliac disease presenting soon after introduction of gluten into the diet. Symptoms frequently include

- diarrhoea
- weight loss or failure to thrive
- anorexia and vomiting
- abdominal pain
- anaemia

Figure 3. Jejunal mucosa showing typical features of coeliac disease: total villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes.



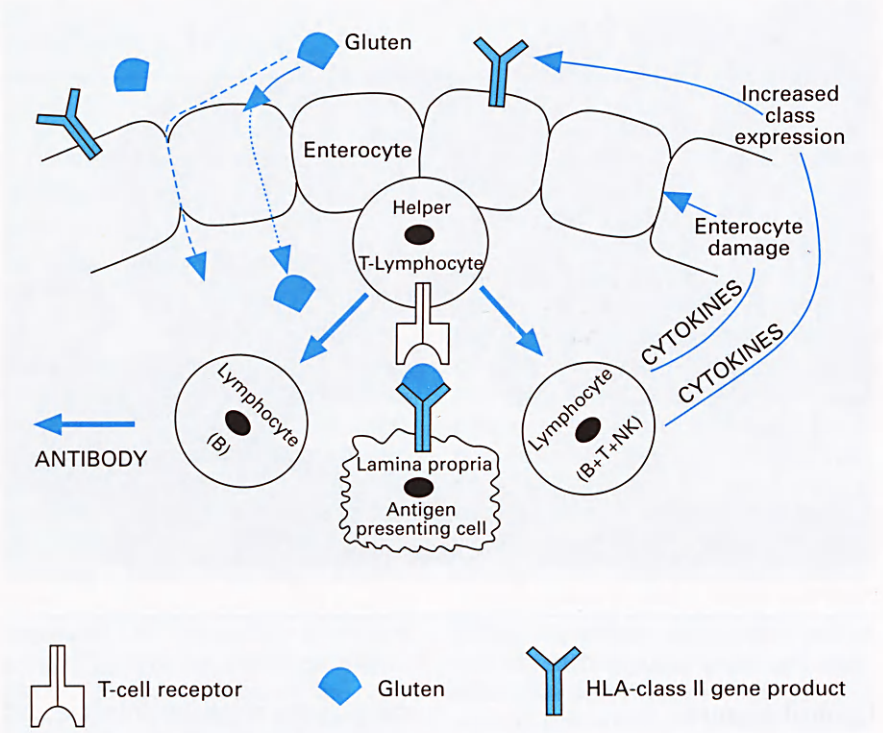


Figure 4. Proposed pathogenic mechanism for coeliac disease. Gluten is absorbed into the lamina propria and presented, in conjunction with HLA class II cell surface antigens, by dendritic cells to sensitised T lymphocytes via the T cell receptor (afferent limb). Release by these T cells of inflammatory mediators, including pro-inflammatory cytokines and nitric oxide, damages the enterocytes (efferent limb) and induces further class II expression (NK = natural killer).

Affected infants and young children often appear pale, apathetic, miserable and irritable and may have generalised hypotonia and abdominal distension. Older children are more likely to have non-specific intestinal symptoms including constipation, or to present with the consequences of long-term untreated disease such as short stature, anaemia or rickets. Short stature in children may result in permanent loss of potential adult height, particularly if diagnosis is delayed until after puberty. Many adult patients have experienced poor health and tolerated intestinal symptoms for many years by the time they are diagnosed and may have signs resulting from chronic illness and malabsorption including anaemic pallor, glossitis, finger clubbing and skin evidence of a bleeding diathesis. Osteoporosis is a problem that is being increasingly recognised at time of diagnosis in both adults and children and patients may present with pathological fractures or symptomatic hypocalcaemia[15]. Neurological or psychiatric symptoms, including schizophrenia and depression, occur more frequently in untreated coeliac disease than the normal population. Female reproductive disturbances include delayed menarche, earlier menopause and amenorrhea. Relative infertility and recurrent abortions are more common but in those who do conceive coeliac disease may be unmasked by the metabolic demands of pregnancy. Low circulating levels of plasma androgens in untreated males may result in delayed puberty or male impotence. Lymphadenopathy and pyrexia are both rare but should raise the suspicion of a complication of the disease such as lymphoma.

Investigations

Haematology

The most common feature is a mild hypochromic, macrocytic anaemia with target cells and Howell Jolly bodies, but a dimorphic anaemia can result from combined iron and folate deficiency. An erythroblastic appearance suggests associated splenic atrophy. At diagnosis, red cell folate levels are reduced in 85% of patients, reflecting reduced total body stores of folate. Vitamin B12 levels are either mildly reduced or lie towards the lower end of the normal range. Bone marrow examination usually shows megaloblastic erythropoiesis, but 55% of patients are also iron deficient and a few exhibit a picture purely of iron deficiency, resulting from impaired absorption, increased losses of iron with rapid epithelial turn over, mucosal blood loss and reduced iron intake associated with poor appetite.

Biochemistry and immunology

Patients with untreated coeliac disease have elevated titres of plasma IgG, IgM and IgA antibodies to wheat gliadin, reticulin and endomysium. Increasingly, these antibodies are being used to undertake population screening, to select more carefully those patients who should undergo a small intestinal biopsy or to support the instigation of a gluten free diet if a biopsy is not possible. In some laboratories the sensitivity and specificity of a combination of anti-gliadin IgG and IgA and anti-endomysial antibodies exceeds 90%[16]. Up to 10% of individuals with coeliac disease have an associated IgA deficiency which may make screening by antibody titres alone unreliable. Asymptomatic individuals with raised antibody titres

will frequently exhibit abnormal small intestinal histology.

Albumin levels are suboptimal in one-third of patients at diagnosis and are often very low in those with lymphoma or jejunal ulceration. Hypocalcaemia and hypomagnesaemia are common and may cause symptoms. Sodium, potassium, zinc and copper deficiencies can result from severe diarrhoea.

Small intestinal biopsy

The current European Society of Paediatric Gastroenterology and Nutrition (ESPGAN) criteria state that the diagnosis can be made on the basis of characteristic histological changes on a small intestinal biopsy, followed by clear-cut clinical remission with relief of all symptoms within a few weeks of starting a gluten free diet[17]. Further biopsies to show mucosal recovery are usually undertaken in adults and should be performed in children if clinical response is equivocal. Gluten challenge is indicated if the diagnosis remains in doubt, particularly if temporary gluten intolerance is likely (under two years of age). The duration of gluten exposure required to produce a clinical or mucosal relapse is difficult to predict, but it is important to avoid gluten challenge in children during periods of accelerated growth.

Endoscopic duodenal biopsies are routinely used for diagnosis in adults, and it is important that at least three optimally orientated specimens are histologically assessed. Suction biopsy of the jejunum (by Watson or Crosby capsule) produces superior tissue samples and reduces the confusion that may be caused by duodenitis or ulceration. The technique is straightforward and complications are rare[14].

Radiology

Routine radiological tests are not indicated unless complicating factors are suspected. The most consistent radiological finding is dilatation affecting both small and large bowel. The jejunum demonstrates loss of its fine feathery folds, seen most clearly on barium follow through investigation.

Other tests

Hydrogen and [^{14}C] breath tests reflect mild small intestinal bacterial overgrowth. Carbohydrate absorption tests are abnormal in most, but not all, patients with untreated coeliac disease[18]. A flat glucose tolerance test and mild lactose intolerance, both of which improve with a gluten free diet, are characteristic. Faecal fat estimations are rarely undertaken, but fat excretion is raised in the majority of untreated patients.

Treatment

Coeliac disease is treated by a diet avoiding wheat, rye, barley and oats. The exclusion of oats is contentious as recent reports question the toxicity of oats[19], although there is a risk of contamination with wheat flour in commercial mills. Patients exhibit varying sensitivity to gluten proteins and there may be a considerable mismatch between symptoms and mucosal changes. It is therefore important to stress the need for a gluten free rather than a *reduced* gluten diet. A range of commercially manufactured gluten free products is available on prescription. The diet's low fibre content may cause symptoms and some individuals need supplementation with iron, folic acid, calcium and occasionally vitamin B12.

Failure to respond to a gluten free diet is usually the result of inadvertent or deliberate non-compliance or the wrong diagnosis. Some individuals are so sensitive to gluten that they will remain symptomatic whilst ingesting commercial 'gluten free' products which may contain very low levels of gluten. This small group of patients should be advised to take a strict gluten free diet in which all products based on wheat starch are excluded. Ulcerative jejunitis or small intestinal lymphoma will develop in 15% of patients with untreated coeliac disease, both requiring appropriate therapy including resection of the affected area.

Corticosteroids may rarely be needed to control severe systemic symptoms or to treat gliadin shock, an anaphylactic reaction that occasionally occurs in sensitive subjects on gluten challenge. Other immunotherapy does not have a place in routine clinical management.

Summary

Coeliac disease, or gluten sensitive enteropathy is a common disorder and results from exposure to gluten in the diet of genetically susceptible individuals. Environmental factors may influence both the age of presentation and the severity of symptoms. Screening by quantifying anti-gliadin and anti-endomysial antibody titres and diagnosis by small intestinal biopsy are both straightforward. A gluten free diet produces clinical and symptomatic improvement and decreases the rate of complications, including gastrointestinal malignancy.

Current research is likely to improve our understanding of the disease pathogenesis, the structure of the toxic cereal peptides, and the genetics of the condition.

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Diagnostic dilemmas in colitis

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Many promising new approaches for medical therapy of inflammatory bowel disease are currently being explored but proven medical therapy has remained essentially unchanged for many years: corticosteroids for acute disease and 5-aminosalicylates for maintenance of remission. Some relatively minor but useful advances have occurred:

- in ulcerative colitis:
  - intravenous cyclosporin in patients with severe colitis who are responding poorly to corticosteroids[1]
  - better evidence for benefit from azathioprine in chronic remitting disease
  - demonstration of the superiority of rectal 5-aminosalicylates over rectal steroids
- in Crohn's disease:
  - clear evidence of a role for metronidazole in colonic and perianal disease[2]
  - better understanding of and evidence for the role of dietary therapy in the primary treatment of small intestinal disease
  - introduction of a delayed release formulation of corticosteroids with rapid first-pass metabolism (budesonide) to reduce the risk of steroid side effects[3].

More significant advances have been made recently in our understanding of the natural history and pathophysiology of the many different forms of colitis, and these should make a considerable impact on clinical management. This article will focus on three areas that commonly cause confusion in diagnosis and where important progress has been made:

1 Overlap between ulcerative colitis and Crohn's disease.
2 Overlap between infective colitis and idiopathic ulcerative colitis.
3 'New' syndromes of collagenous, lymphocytic (microscopic) and diversion colitis.

Overlap between ulcerative colitis and Crohn's disease

The traditional approach to the difficulties in distinguishing ulcerative colitis from Crohn's disease has been dogmatic adherence to a set of widely quoted 'typical' clinical, radiological, endoscopic and pathological criteria which 'define' the diagnoses:

- *Colonic Crohn's disease* if some or all the following are present: granulomas (found in 60–70%), inflammation deep to the muscularis mucosae, goblet cell retention in the presence of inflammation, rectal sparing, skip lesions, perianal fistulae, sinuses or skin tags.
- *Ulcerative colitis* if there is continuous disease extending proximally from the rectum, superficial inflammation with goblet cell depletion, and absence of small intestinal inflammation (apart from mild 'backwash' ileitis in total colitis).

Using such criteria, approximately 10–15% of patients with colitis are left 'unclassifiable' with some features of both conditions – and may then be told that no firm diagnosis can be made. Furthermore, although some specialists will accept the presence of granulomas in up to 4% of patients with ulcerative colitis[4], more commonly the discovery of a granuloma at routine colonoscopic biopsy in a patient with otherwise typical ulcerative colitis leads to a change in diagnosis to Crohn's disease – often