Coeliac disease

Jeremy Woodward

Abstract

Coeliac disease is a common condition that affects up to 1% of Caucasian and North West Asian populations. It may present at any age after weaning with a spectrum of symptoms ranging from none, through mild irritable bowel type complaints, to weight loss and diarrhoea. Coeliac disease is often associated with other autoimmune conditions. The majority of patients express either HLA DQ2 or DQ8 haplotypes, but many other genes (some of which have recently been identified) are implicated in disease susceptibility. IgA antibodies against tissue transglutaminase show a high specificity but a sensitivity that may be as low as 90% for detection of the condition. Intestinal biopsy remains the diagnostic standard. Treatment with a strict gluten-free diet is mandatory and leads to a reduced risk of associated complications that include low bone mineral density and intestinal malignancy. Most patients thought to be 'refractory' to dietary treatment are found to have gluten sources in the diet, but a small proportion harbour atypical monoclonal intraepithelial lymphocytes and are at risk of developing intestinal lymphoma. Non-dietary treatments are currently under investigation.

Keywords Anaemia; coeliac disease; enteropathy-associated T-cell lymphoma; gluten; malabsorption; osteoporosis; refractory sprue; tissue transglutaminase

What's new?

- Recent studies have investigated innate immune recognition of gliadin peptides that may trigger or enhance adaptive T-cell responses through epithelial production of interleukin-15, and increase epithelial permeability by increased expression of zonulin
- Novel non-dietary therapies are being explored including:
  - the use of oral endopeptidases to digest gliadin peptides
  - the use of oral zonulin receptor antagonists
  - 'blocking' peptides to prevent TTG deamidation of gluten or binding of peptides to HLA DQ2
  - 'immunization' by systemic exposure to immunodominant gliadin peptides

Coeliac disease results from damage to the small intestinal mucosa due to an inappropriate immune response to a cereal protein. The term 'coeliac' derives from the Greek 'koiliakos', meaning 'belly'.

Epidemiology

Coeliac disease is a common condition that affects 0.3–1% of Caucasians.[1] A high prevalence also occurs in North African and Middle Eastern populations. It is largely confined to the Northwest of the Indian subcontinent and is rarely reported in oriental or black African peoples.

A slightly higher incidence in females than males possibly relates to the likelihood of detection as a result of iron deficiency, or associated autoimmunity.

Coeliac disease can present at any age after weaning. Whilst commonly diagnosed in early childhood, it can remain subclinical or 'latent' for considerable periods of time — nearly one-third of patients describe a delay of over 10 years from first symptoms to diagnosis. Approximately 10% of first-degree relatives are affected.[2]

Pathology

The enteropathy of coeliac disease is predominantly proximal. The characteristic lesion is described as 'villous atrophy'. However, except in very severe disease, the intestinal mucosa is far from atrophic, being expanded by a chronic inflammatory infiltrate in the lamina propria and hyperplasia of the crypts, in which stem cells are stimulated to divide in order to replenish surface enterocytes. Intraepithelial lymphocytes (IELs) are increased in number and may persist after resolution of other changes (Figure 1).[3]

Pathogenesis

The toxic factor

'Gluten' is the generic term used for the protein fraction of cereal grains that causes coeliac disease, being present in wheat, barley and rye. Many different gluten proteins have been identified and characteristically contain a large amount of proline and glutamine residues. These may confer unique properties on gluten peptides including resistance to luminal proteolysis. Gluten is not found in rice, maize or millet. However, the toxicity of oats remains controversial — cross-contamination with other cereals at the time of milling may account for most reports of oats causing coeliac disease.

Host factors

The ability to mount an immune response to gluten depends on the presentation of gluten peptides to T cells. This requires prior deamidation of the glutamine residues of the peptide by tissue transglutaminase (TTG), a ubiquitous connective tissue enzyme.[4] Few class II major histocompatibility (MHC) proteins are capable of presenting gluten peptides — hence, over 90% of patients with coeliac disease express HLA DQ2, and 5–10% express HLA DQ8.[5]

As approximately 20% of Caucasians express HLA DQ2, other factors must be required in order to develop coeliac disease. HLA haplo-identical siblings have a concordance rate of 40%[6] compared with around 75% for identical twins,[7] suggesting a large non-HLA genetic component. Recent large-scale genome-wide association studies have identified over 30 regions harbouring candidate-susceptibility genes.[8] The majority of these affect immune functions and include genes such as interleukin 2 and 21, interleukin 18 receptor, and others with innate immune functions, such as SH2B3. Many such loci are shared with other autoimmune conditions including type 1 diabetes mellitus and rheumatoid disease, explaining a shared propensity.

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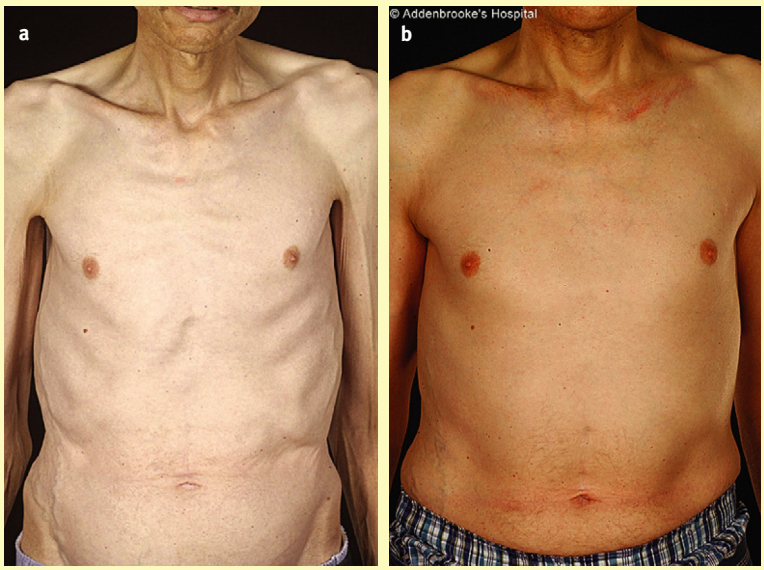

a This 47-year-old man who was being investigated for osteomalacia and weight loss also complained of steatorrhoeic motions, abdominal bloating and discomfort. The blood count revealed a slightly low haemoglobin (11.3 g/dl) with normal mean cell volume (91.2 fl). Red blood cell folate, serum vitamin B_{12} and ferritin concentrations were within normal range. The serum albumin was normal at 35 g/dl, but the corrected calcium concentration was 1.88 mmol/l (normal range 2.1–2.5 mmol/l), serum alkaline phosphatase was elevated at 299 u/l (normal range 30–135 u/l) and the alanine aminotransferase at 180 u/l (normal range 0–50 u/l). The serum parathyroid hormone concentration was 284 ng/l (normal range 9–54 ng/l) and the vitamin D concentration was 8.1μg/ml (normal seasonal range 9–47). The IgA anti-TT G titre was >100 iu/l (normal 0–3 iu/l). **b** Following initiation of a gluten-free diet his body weight increased from 50 kg to 70 kg over four months with resolution of the diarrhoea and abdominal symptoms. The liver enzymes and parathormone concentrations returned to normal ranges.

Figure 1 The profound potential consequences of coeliac disease.

End-organ damage

T-cell activation following recognition of the gluten peptide results in damage to the intestinal mucosa by the direct action of inflammatory mediators and by matrix metalloproteinase enzymes secreted by stimulated fibroblasts.[9] The ensuing reduction in absorptive capacity can result in malabsorption of fat- and lipid-soluble vitamins (A, D, E and K), as well as iron, folate and calcium.

Clinical features

Coeliac disease is frequently asymptomatic, but patients without symptoms may notice increased well being after diet initiation. The classical presentation in early childhood is with profuse diarrhoea and failure to thrive after weaning, but subtle features may occur in older children, such as reduced growth velocity or impaired performance at school.

- Diarrhoea may be clearly steatorrhoeic owing to fat malabsorption. However, gastrointestinal symptoms may be minimal, and bloating and discomfort may be misdiagnosed as irritable bowel syndrome.[10]
- Weight loss may be significant (see Figure 1), but is frequently absent and obesity does not exclude the diagnosis.
- Fatigue and depression are common.
- Iron deficiency may result in symptomatic anaemia but is frequently detected coincidentally (for instance, at blood donor sessions).
- Anaemia may also be the result of folate or vitamin B_{12} deficiency.
- Neurological presentations, including peripheral neuropathy, epilepsy and ataxia, are described.
- Vitamin D deficiency causes rickets in childhood and osteomalacia in adults, and may present with fractures, or proximal muscle pains and weakness.

Investigations

Routine laboratory investigations may reveal a low haemoglobin concentration with microcytosis, and Howell–Jolly bodies may be present on the blood film. Serum folate and vitamin B_{12} may be low. A reduced serum calcium and raised serum alkaline phosphatase may result from vitamin D deficiency. An elevated serum transaminase (ALT or AST) is common at presentation.[11]

Quantification of serum IgA antibodies against tissue transglutaminase (TTG) has a very high specificity for the diagnosis of coeliac disease (>95% depending on the cut-off level), but a sensitivity that may be as low as 90%.[12,13] It may also aid the monitoring of dietary compliance. TTG antibody testing has largely superseded endomysial antibody testing owing to ease of assay.

Intestinal biopsy is considered mandatory for the diagnosis of coeliac disease in adults, and is usually obtained by gastroscopy, during which scalloped, thickened duodenal folds may be seen. Recent guidelines suggest that the diagnosis can be made in children without an intestinal biopsy when the anti-TTG antibody titre is more than ten times the upper limit of normal.[14]

