The changing face of coeliac disease

Coeliac disease was considered to be a rare childhood affliction causing malabsorption and weight loss. It is now recognized to occur at any age with a range of non-specific manifestations including anaemia, recurrent miscarriages, neuropsychiatric disorders and osteopenia. This article summarizes advances in diagnosis and innovations in therapy.

The Dutch paediatrician Willem K Dicke (1941) was the first to recognize that there was an association between the consumption of bread and cereals, and the onset of diarrhoea. This observation was corroborated by the Dutch famine during the Second World War, when the symptoms of those affected improved with the introduction of non-cereal containing foods.

Dicke, and his colleague van de Kamer, studied these observations further by initiating controlled experiments on affected children, exposing them to defined diets and measuring stool weight and fat content as markers of malabsorption (Smits, 1989). Wheat, barley and rye were found to cause malabsorption, which could be reversed on dietary exclusion. The toxic agent, gliadin, was subsequently found to be present in gluten, the alcohol-soluble fraction of wheat protein.

The histological lesion in the proximal small intestine was first described in 1954. The primary findings are mucosal inflammation, crypt hyperplasia and villous atrophy (Paulley, 1954). Gliadin induces a T-cell mediated inflammatory response in genetically predisposed individuals, provoking inflammation and villous atrophy.

Genetic factors are suggested by the 70% concordance in identical twins, and a prevalence of 10–15% in siblings (Kagnoff, 1992). HLA studies indicate that most coeliacs possess the extended haplotype DR3-DQ2, DR5/7-DQ2, or less often DR4-DQ8 (Schuppan, 2000). Antigen-presenting cells bearing these HLA haplotypes present gliadin peptides to intestinal mucosal T cells, which mediate the immune response through cytokines such as interleukin-15 (IL-15) and interferon gamma. Tissue transglutaminase (TTG), a ubiquitous intracellular enzyme released by inflammatory cells and fibroblasts, modifies gliadin to promote antigen presentation (Molberg et al, 1998).

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The burden of coeliac disease

Coeliac disease affects white Europeans, primarily of celtic ancestry. Coeliac disease was previously thought to be rare, on the basis of clinical frequency, affecting 1 in 3000 people worldwide. However, the advent of serological testing has shown the worldwide prevalence to be 1 in 266 (Not et al, 1998). Thus, a vast population of patients exist, who were previously thought to be asymptomatic, but are now recognized to have non-specific symptoms and be subject to the same risks and complications as those with 'classical' disease.

Coeliac disease can also affect non-European populations if they have an appropriate genetic background. Punjabi and Gujarati migrants living in England develop the disorder 2.7 times more commonly than Europeans when on a gluten-rich diet (Sher et al, 1993). A disorder named 'summer diarrhoea' has long been known in India, when wheat replaces maize during the summer season.

The mortality rate in coeliac disease exceeds that of the general population by a factor of 1.9–3.8, which is mainly a result of malignant disease (Corrao et al, 2001). The reduction in excess mortality after 1–5 years on a gluten-free diet suggests that such a diet is protective against malignancy. This notion is supported by a Finnish study that showed patients on a strict gluten-free diet had no greater frequency of death than those of the general population (Collin et al, 1994).

Clinical features

Coeliac disease is a disorder of the proximal small intestine that can involve the entire small intestine in some individuals. This proximal location in the small intestine often results in malabsorption of iron, folic acid, calcium and fat-soluble vitamins, with resultant nutrient deficiencies and reduced bone density. Diarrhoea, the hallmark of classical disease, is a result of progression of disease to the distal small bowel. If only the proximal small bowel is involved, then the distal small bowel is able to compensate and absorb the products of fat and carbohydrate digestion. Pregnancy, traveller's diarrhoea, gastroenteritis or gastrointestinal surgery can act as a trigger for the development of symptoms.

Infants and young children present with diarrhoea, abdominal distension and failure to thrive. However, vomiting, irritability, anorexia and constipation are also common.

Diarrhoea remains the most common presenting symptom in adults, but accounts for less than half of all

presentations. Patients frequently have a long duration of symptoms, with a mean time to diagnosis of 11 years (Green et al, 2001). In the interim, patients often receive an alternate diagnosis, such as irritable bowel syndrome.

Extra-intestinal manifestations have been described, and are frequently the presenting complaint (*Table 1*). These include dermatitis herpetiformis, obstetric and neurological symptoms. Dermatitis herpetiformis is an intensely pruritic vesicular rash, occurring anywhere on the body but especially on the extensor surfaces and the scalp. The diagnosis is confirmed by the demonstration of granular immunoglobulin A (IgA) on the subepidermal basement membrane. Dapsone controls these skin lesions, although the majority resolve on a gluten-free diet.

A variety of gynaecological and obstetric presentations are associated with coeliac disease, including delayed menarche, infertility, miscarriages, intrauterine growth retardation and low birthweight (Ludvigsson et al, 2005). Furthermore, studies have suggested an association between coeliac disease and neurological syndromes. The neurological presentations are varied, from peripheral neuropathy or ataxia to neuropsychiatric syndromes such as depression, anxiety or epilepsy (Hadjivassiliou et al, 1996). However, these associations remain the subject of debate, since causality between these common syndromes is yet to be proven.

Non-classical disease

The sub-clinical form of coeliac disease has become apparent since the development of serological testing. These patients often remain undetected, since they experience mild, non-specific symptoms such as fatigue, unexplained iron deficiency, unexplained elevations in serum transaminase levels or no symptoms at all. Establishing the diagnosis of sub-clinical coeliac disease is of potential importance for four reasons: the risk of potential malignancy; the presence of unsuspected nutritional deficiencies; the association with low-birth weight infants in affected mothers; and the occurrence of autoimmune disorders.

Table 1. Non-malignant complications of coeliac disease

Infertility	
Rheumatic disorders	
Vitamin D and calcium deficiency	Osteomalacia
	Osteoporosis
Neurological disorders	Depression (10.6%)
	Epilepsy (3.5%)
	Migraine headaches (3.2%)
	Anxiety (2.6%)
	Suicidal tendency (2.1%)
	Carpal tunnel syndrome (1.8%)
	Myopathy (1.5%)

Modified from Holmes (1996)

The risk of malignancy in patients with sub-clinical coeliac disease is not known, although it appears to be lower than in patients who present with malabsorptive symptoms. However, once the disease is in remission, on a gluten-free diet, the risk approaches that of the normal population (Collin et al, 1994). The prevalence of autoimmune disease, such as type 1 diabetes mellitus and autoimmune thyroiditis, appears to be related to the duration of undetected coeliac disease (Ventura et al, 1999).

Diagnosis

Coeliac disease is diagnosed in the presence of characteristic changes on a small intestinal biopsy sample, and improvements in clinical symptoms or histology after 4–6 months on a gluten-free diet. Positive serological tests support the diagnosis, but are not essential.

Duodenal biopsy should be considered in several circumstances:

- Gastrointestinal symptoms including chronic diarrhoea, malabsorption, weight loss and abdominal distension
- Iron-deficiency anaemia
- Osteopenia
- Short stature
- Delayed puberty
- Elevation of serum transaminase levels
- Recurrent fetal loss and infertility
- Peripheral neuropathy and cerebellar ataxia.

Detection of IgA antibodies against TTG has a sensitivity of 95% and specificity of 96% for the diagnosis of coeliac disease (Sugai et al, 2006). However, this should not replace small intestinal histology, which is required both to confirm the diagnosis and as a baseline from which to monitor improvement.

Pitfalls in the diagnosis of coeliac disease

Selective IgA deficiency occurs in 2.6% of patients with coeliac disease, ten-fold higher than that in the general population (Cataldo et all, 1998). Thus, individuals with selective IgA deficiency and coeliac disease will not have anti-TTG antibodies, although these patients will have a raised total IgG concentration. The diagnosis therefore rests upon measuring the serum IgA, and specific anti-endomysial and anti-TTG IgG antibody tests. The combination of IgA deficiency and a positive IgG test should prompt a biopsy.

The amount of dietary gluten, the presence of symptoms, the degree of villous atrophy and the concomitant use of immunosuppressants influence titres of anti-TTG antibodies. Therefore, serological testing alone will significantly underestimate the prevalence of coeliac disease. Antibody titres are usually undetectable after 6–12 months

on a gluten-free diet, but can still be detected for up to 31 months if the initial titres are high. Seroconversion precedes histological improvement.

The major pitfall of histological diagnosis is biopsy interpretation. Adequate numbers of biopsies are required, since the disease is patchy and the biopsies need to be oriented correctly to interpret the crypt to villous ratio. As a rule, at least three well-oriented crypts need to be identified to interpret villous atrophy. The differential diagnosis of villous atrophy includes post-gastroenteritis, giardiasis, peptic duodenitis, tropical sprue and Crohn's disease. Negative serological tests or poor response to a gluten-free diet should prompt review of the biopsy to ensure that the original interpretation was correct.

Wheat intolerance

A beneficial response to a gluten-free diet does not necessarily indicate coeliac disease, since it is not unusual for patients with irritable bowel syndrome to benefit from such a diet. The placebo response of a gluten-free diet among patients with irritable bowel syndrome is up to 70% (Horwell and Lea, 2004). Furthermore, a gluten-free diet often coincidentally eliminates other dietary factors which cause digestive discomfort.

Conversely, the prevalence of coeliac disease is 3–4% among populations with irritable bowel syndrome (Sanders et al, 2001). Thus, coeliac serology must be performed in the workup of patients with even non-specific gastrointestinal symptoms.

Confirming the diagnosis

Individuals with uncharacteristic histology – such as increased intraepithelial lymphocytes without villous atrophy or crypt hypertrophy – or seronegative patients with typical histology, should undergo gluten challenge to confirm the diagnosis. Following a diet of at least 10 g of gluten daily for at least 6 weeks (equivalent to four slices of bread daily), biopsies are obtained when the patient develops positive serology or symptoms.

Assays to detect HLA DQ2 and DQ8 have made genetic testing possible for those at risk of coeliac disease, or those with equivocal histology and serology. While these alleles are present in 35–40% of caucasian populations, they are almost universal among populations with coeliac disease (Kaukinen et al, 2002).

Treatment

Lifelong avoidance of dietary gluten is an austere yet effective therapy for sufferers of coeliac disease. Thus, religious adherence to such a diet must not be on the basis of blind faith, but should follow a definitive, biopsy-proven diagnosis.

Dietary counselling is the cornerstone of treatment for coeliac disease. Gluten is a common constituent of the western diet, and complete avoidance is a significant challenge. Written information and dietary counselling are essential to promote compliance. Further resources include patient groups such as Coeliac UK, internet sites, gluten-free cookbooks and gluten-free prepared foods. Gluten-free products are available on prescription, which should be on FP10 forms clearly marked ACBS, an abbreviation for 'according to the borderline substances act'. Specialist products include bread, biscuits, flour, pasta, crackers, pizza bases and cakes. Luxury items can also be obtained from supermarkets and health food shops. Coeliac UK also provide the magazine *Crossed-Grain*, which provides support and recipes, promoting variety and helping to improve both compliance and quality of life.

Barley and rye should be avoided, as well as wheat, since these grains share a similar taxonomy and may all induce symptoms. Oats are of a different taxonomy to wheat, barley and rye, and do not have gliadin as their major protein. Pure oats are therefore considered safe in coeliac disease. However, many patients experience symptoms if eating commercially available oats, which are likely to be the result of contamination with other grains, and these should therefore be avoided.

Potatoes, rice, fruits, vegetables, maize, corn, soya, eggs and dairy produce are all safe, and should be positively highlighted. Particular attention should be given to food labels, and also to additives, since stabilizers and emulsifiers may also contain gluten. A gluten-free diet may induce constipation because of the lack of roughage. This usually responds to dietary rice bran and ispaghula husk.

Nutritional and calorific deficiencies must be sought and appropriately supplemented. Specific dietary deficiencies such as iron, folic acid, calcium, vitamin D and, rarely, vitamin B_{12}, should be corrected.

Bone loss is common in coeliac disease, and can occur in patients without gastrointestinal symptoms. Much of the bone loss is related to secondary hyperparathyroidism, a consequence of vitamin D deficiency. It is only partly corrected by a gluten-free diet, and may persist despite normal serum calcium and alkaline phosphatase values. All patients should have their bone mass assessed by dual energy X-ray absorptiometry at diagnosis. All patients should receive calcium and vitamin D supplementation, and appropriate osteoporosis treatment as determined by their bone density.

Coeliac disease is also associated with hyposplenism, hence patients should be immunized with pneumococcal vaccination.

Non-adherence is the most common cause of ongoing symptoms after the introduction of a gluten-free diet. Many patients consider their symptoms to be sufficiently mild as to not warrant the sacrifice of gluten avoidance and lifestyle change. This opinion is even more common among asymptomatic patients, in whom coeliac disease was diagnosed following antibody testing. However, regardless of clinical symptoms, the previously stated arguments favour the strict adherence to a gluten-free diet in patients with established coeliac disease. Despite feel-

ing clinically well, patients may have a variety of micronutrient deficiencies that may have clinical sequelae, such as bone loss or anaemia (Shaker et al, 1997). These patients also have increased mortality compared to the general population, predominantly as a result of gastrointestinal malignancy, which recedes with adherence to a gluten-free diet (Corrao et al, 2001). The likelihood of developing associated autoimmune disease may also be related to the duration of exposure to gluten (Ventura et al, 1999). Furthermore, mothers with untreated coeliac disease are at increased risk of having children of low birthweight or with neural tube defects (Ludvigsson et al, 2005).

Further counselling with an experienced dietician, and meticulous food diary monitoring, are appropriate at this stage.

Other considerations in patients who do not respond to gluten avoidance are: a secondary diagnosis; refractory coeliac disease; or intestinal lymphoma. Irritable bowel syndrome, lactose intolerance or small bowel bacterial overgrowth are frequent secondary diagnoses. Refractory disease or suspected lymphoma often requires inpatient assessment by a gastroenterology multidisciplinary team.

Conclusions

Coeliac disease has undergone a metamorphosis from a rare disorder of infancy to a silent epidemic with lifelong consequences. The cornerstones of management in both primary care and outpatient settings are a long-term relationship with physicians and dieticians, patient education and lifelong support. **BJHM**

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KEY POINTS

- Coeliac disease is no longer considered to be a rare disorder of infancy, but a common condition with lifelong clinical consequences.
- Diagnosis and treatment is necessary to prevent nutritional deficiencies, metabolic bone disease and obstetric complications, and to reduce mortality from malignancy.
- Serological tests for coeliac disease are adequate screening tools, but should not replace small intestine histology as a baseline for diagnosis and initiating a gluten-free diet.
- Adherence to a gluten-free diet is the cornerstone of treatment. Dietary counselling must form an integral part of the multidisciplinary approach to management.