An update on coeliac disease

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This review article provides an overview of coeliac disease but also highlights its protean manifestations. These can often lead to a delay in diagnosis of this easily treatable condition.

Coeliac disease, or gluten sensitive enteropathy, is characterized by typical histological changes in the small intestine caused by the gliadin fraction of wheat gluten and similar alcohol-soluble proteins (prolamines) of barley and rye in genetically susceptible individuals. Coeliac disease is a true autoimmune disease for which the genetic predisposition (HLA DR3 and HLA DQ2), environmental trigger (gluten or prolamine) and autoantigen (tissue transglutaminase) are known. The disease is self-perpetuating in the continued presence of gluten in the diet, but the typical intestinal changes resolve completely on a strict gluten-free diet. It is now established that coeliac disease is the result of an inappropriate T-cell-mediated response against ingested gluten (Schuppan, 2000).

EPIDEMIOLOGY

Over the years, the clinical presentation of coeliac disease has changed considerably. Previously, cases were diagnosed when they presented with the classical malabsorption syndrome comprising chronic diarrhoea, weight loss or failure to thrive, and short stature. Recent studies worldwide have shown that extra-intestinal symptoms are 15 times more common in newly diagnosed coeliac disease than the classical gastrointestinal symptoms; in fact, a large proportion of patients are asymptomatic.

We are therefore seeing only the tip of the coeliac iceberg (as conceptualized by Logan in 1990), and for each diagnosed case of coeliac disease, an average of 5–10 cases remain undiagnosed (Fasano and Catassi, 2001). Population screening studies have shown that the prevalence of coeliac disease is as high as 1 in 130–300 in the European population (Kolho et al, 1998). Coeliac disease will remain underdiagnosed unless high-risk individuals are screened for this disorder (Unsworth and Brown, 1994).

CLINICAL PRESENTATION

Classical

This is typically seen between 6–18 months of age, shortly after the introduction of weaning foods, and is characterized by chronic diarrhoea (stools are characteristically pale, loose, bulky and foul smelling because of fat malabsorption), failure to thrive, anorexia and vomiting, abdominal pain and distension, and muscle wasting.

Atypical

Coeliac disease in adult life may present with involvement of almost any system of the body, and the diagnosis should be considered in the following situations:

1. Iron deficiency anaemia, typically unresponsive to oral iron supplementation
2. Short stature
3. Osteopenia or osteoporosis
4. Recurrent abdominal pain or bloating – often mistakenly attributed to irritable bowel syndrome
5. Dental enamel hypoplasia
6. Recurrent mouth ulcers
7. Isolated raised alanine aminotransferase levels
8. Arthritis and arthralgia
9. Recurrent abortion and reduced fertility
10. 'Tired all the time' syndrome
11. Unexplained hypocalcaemia
12. Unexplained neurological or psychiatric problems.

Asymptomatic

Most cases are identified through screening programmes of apparently healthy subjects. A study was undertaken involving adolescents with screening-detected coeliac disease who were apparently symptomless on diagnosis. Subjects often reported improved physical and psychological wellbeing once they began a gluten-free diet (Fabiani et al, 1996). The most common changes included increased weight and height velocity, increased appetite, mood amelioration and improved physical and school performance.

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DIAGNOSIS

The revised criteria for the definitive diagnosis of coeliac disease proposed by the European Society of Paediatric Gastroenterology and Nutrition (Walker-Smith et al, 1990) are as follows:

1. History and clinical presentation compatible with coeliac disease
2. Serological screening compatible with coeliac disease
3. Histological findings compatible with coeliac disease
4. Obvious clinical and serological response to gluten-free diet
5. Subject >2 years old*
6. Rule out other clinical condition mimicking coeliac disease.

Serological tests

The most commonly used serological screening tests are combined immunoglobin (Ig) G and IgA antigliadin antibody (AGA) and IgA antiendomysial antibody (AEA). IgG AGA has good sensitivity, and IgA AGA has good specificity, although not as high as AEA, which has a specificity approaching 90%. However, AEA assays are costly and have poor sensitivity in young children less than 2 years of age and in IgA-deficient individuals (who have a 10-fold increased risk of associated coeliac disease) (Cataldo et al, 1998).

The search for a simple, efficient screening tool continues, and the report of human tissue transglutaminase (tTG) dot blot tests, based on the detection of anti-tTG antibodies in serum or in 1 drop of whole blood within 30 minutes, is highly encouraging (Baldas et al, 2000).

Histological findings

Diagnosis of coeliac disease is confirmed by proximal small intestinal biopsies (usually duodenal) obtained at endoscopy. It is important that at least three optimally orientated specimens are histologically assessed. The severity of the histological changes decreases distally as the gluten is hydrolysed and becomes less toxic. Typical histological features described are:

- Mucosal atrophy ranging from partial to total absence of villi
- Crypt hyperplasia (normal ratios of villous height to crypt depth are reduced from between 3:1 and 5:1 to between 1:1 and 1:2, Morris and Ciclatara, 1997)
- Increase in the number of intra-epithelial lymphocytes and marked infiltration of the lamina propria with plasma cells.

A second duodenal biopsy to show histological improvement is considered mandatory if the child was less than 2 years of age at the time of diagnosis and is recommended in adults. If the diagnosis is in doubt, duodenal biopsies should be obtained after a formal gluten challenge. This should comprise at least 10 g of gluten (four slices of normal bread) per day for a minimum of 2 weeks in adults and for 6 weeks in the case of children (British Society of Gastroenterology, 1996).

LABORATORY FINDINGS

1. Hypochromic, microcytic anaemia, secondary to iron deficiency
2. Dimorphic anaemia from combined iron and folate deficiency (vitamin B_{12} levels are usually preserved as intestinal changes are least marked in the terminal ileum from where vitamin B_{12} is absorbed)
3. Raised alanine aminotransferase levels
4. Hypocalcaemia
5. Hypoalbuminaemia
6. Vitamin D deficiency (15–30%)
7. Vitamin K deficiency (10%).

ASSOCIATED CONDITIONS

- Dermatitis herpetiformis†
- Trisomy 21 (Down's syndrome)
- Insulin-dependent diabetes
- Autoimmune thyroid disease
- Inflammatory bowel disease
- Chronic active hepatitis
- Other autoimmune conditions.

TREATMENT

A strict lifelong gluten-free diet is the cornerstone of treatment for the disease. A marked symptomatic improvement may occur within several days, but full recovery of mucosal histology may take up to 2 years. Wheat, rye and barley are the predominant grains that need to be avoided. It is now believed that oats, once considered toxic for patients with coeliac disease, can be ingested safely in adults (Janatuinen et al,

*In children less than 2 years of age, other causes of enteropathy (e.g. cow's milk protein intolerance, transient gluten intolerance, post-enteritis syndrome) often cause diagnostic difficulties.

†Dermatitis herpetiformis can be considered an extra-intestinal manifestation of coeliac disease. It occurs in 2–5% of cases of coeliac disease and presents typically with an intensely pruritic, blistering rash frequently affecting the knees, elbows, buttocks and back. Diagnosis is dependent on the demonstration of immunoglobulin A deposits in uninvolved skin. Patients should be started on a strict gluten-free diet, but this may take about 6 months to show a response and up to 2 years for complete healing of the rash. The rash can be treated in the meantime with dapsone or alternatively with sulphapyridine.

1995). However, cross contamination of oats with gluten in the harvesting and milling procedure remains a problem, and many physicians continue to exclude oats from the diet of their coeliac disease patients. Even small amounts of gluten inadvertently ingested (e.g. in medication or vitamin and mineral supplements) may lead to a persistent enteropathy, and thorough dietary review by an expert dietician is mandatory. Dietary compliance may be monitored by means of the anti-endomysial antibody, which becomes negative in the absence of gluten and on reversal of the villous atrophy.

Gluten-free products (flour, bread, biscuits and pasta) are available on prescription from general practitioners. FP10 prescription forms should be used marked ACBS, an abbreviation for 'according to the borderline substance act'. Most of these products are based on purified wheat starch from which most gluten proteins have been removed. A minority of patients with coeliac disease will be unable to tolerate these products. Their diet should include only commercial non-wheat starch-based gluten-free products. Malt is also toxic because it is a partial hydrolysate of barley prolamines, and patients need to be aware of the potential problems with malt flavouring in cornflakes, traditionally thought to be safe in coeliac disease.

COMPLICATIONS OF COELIAC DISEASE

There are a number of different complications of coeliac disease, as listed in *Table 1*.

Malignancy

The overall mortality in coeliac disease is twice that of the general population (Logan et al, 1989), mainly because of the occurrence of neoplasms, particularly intestinal lymphoma. Holmes et al (1989) found a two-fold risk of developing cancer in a study of 210 coeliac disease patients, with a relative risk of developing non-Hodgkin's lymphoma of about 40. These rates returned to normal after 5 years on a gluten-free diet. This is the main reason why even asymptomatic patients should be encouraged to follow a strict gluten-free diet. This is supported by data from Logan et al (1989), who found that mortality rates in children with coeliac disease who followed a strict gluten-free diet were not different from those expected in the general population, and there were no reported deaths from intestinal lymphomas.

TABLE 1.
Complications of coeliac disease

Malignancy
Ulcerative jejunitis
Disorders of bone metabolism
Reduced fertility
Splenic atrophy (Howell–Jolly bodies on blood film)

The lymphoma associated with coeliac disease is of T-cell origin and is referred to as 'enteropathy-associated T-cell lymphoma' (EATCL). The prognosis for EATCL is usually very poor, as the disease is often widespread at presentation. Patients not known to have coeliac disease may present as an acute emergency with obstruction or perforation. EATCL should also be suspected in coeliac disease patients previously controlled on a gluten-free diet who have a recurrence of symptoms, such as diarrhoea, weight loss and lethargy. Small intestinal biopsies should be repeated, and imaging should include small bowel contrast radiology and computed tomography scanning. On occasions, a laparoscopy or even a laparotomy with lymph node, liver or full thickness intestinal biopsies may be necessary to confirm the diagnosis. Treatment of EATCL includes surgery, chemotherapy and radiotherapy, but survival rates are very poor.

Other malignancies reported include small intestinal and colon adenocarcinomas and cancers of the mouth, pharynx and oesophagus.

Ulcerative jejunitis

This is an unusual complication in which unresponsive coeliac disease is associated with ulceration (usually transverse) and stricturing in the

CASE HISTORY

A now 36-year-old female first presented in 1990 with what appeared to be a food intolerance to mainly potatoes, carrots and chickpeas. Her symptoms of diarrhoea and bloating settled on an exclusion diet. In 1993, she developed bacillary dysentery following travel abroad with a recurrence of diarrhoea, which once again settled spontaneously. The year before she had a course of oral iron as she was found to be slightly anaemic.

She became unwell shortly after the birth of her first child in 1995 with severe diarrhoea, exhaustion (normal full blood count), nausea and aching joints. She was unable to cope with the physical effort of looking after her child and became increasingly depressed. She was commenced on antidepressants and her profound tiredness was attributed to a chronic fatigue syndrome. Extensive investigations at the time, including thyroid function, tests of adrenal function, autoantibody screens, sex hormone profiles, complement fixation antibody tests and serology for *Borrelia*, *Brucella* and *Yersinia* infections, were negative. By 1999, she was largely bed and wheelchair bound and dependent on home help support. In early 2000, she was found to have positive anti-gliadin antibodies, and coeliac disease was confirmed on duodenal biopsies. She responded within weeks to a gluten-free diet and is currently in perfect health.

small bowel. A severe malabsorption syndrome with diarrhoea and weight loss is the usual presentation. Differentiation from a lymphoma is often only possible at laparotomy with full thickness biopsies or resection. Surgical resection can be curative especially if the disease is localized. Steroids have been used with some success, although there have been reports of intestinal perforation following steroid treatment (Baer et al, 1980).

Disorders of bone metabolism

Osteoporosis, osteopenia and, to a lesser extent, osteomalacia are increasingly being recognized in coeliac disease. Osteoporosis is defined as a bone mineral density > 2.5 standard deviations below the mean for a young adult. Osteoporosis carries a significant fracture risk, particularly in post-menopausal women, and therefore screening of coeliac disease patients with dual energy X-ray absorptiometry (DEXA) to determine bone density is now recommended. General advice, apart from a strict gluten-free diet for the prevention of osteoporosis, should include regular exercise (particularly weight-bearing), no smoking or alcohol excess. A total daily calcium intake of 1500 mg is recommended (a pint of semi-skimmed milk contains 700 mg). The possibility of vitamin D deficiency should be investigated, particularly if the alkaline phosphatase levels are raised, as osteomalacia is often asymptomatic.

Treatment for established osteoporosis includes oral biphosphonates or calcitonin and in post-menopausal women hormone replacement therapy (preferably by means of skin patches). Treatment should be continued for at least 3 years if there is no deterioration in the bone density scans, which should be performed annually (Scott et al, 2000).

TABLE 2.
Causes of persistent diarrhoea in coeliac disease patients

Pancreatic insufficiency
Secondary lactase deficiency
Other food intolerances (e.g. milk, soya, egg)
Bacterial overgrowth
Giardiasis
Coexisting inflammatory bowel disease
Collagenous colitis
Lymphocytic colitis
Zinc deficiency

NON-RESPONSIVE COELIAC DISEASE

A minority of adult patients with coeliac disease do not respond to treatment with a gluten-free diet. The most likely cause is continued inadvertent gluten ingestion (often indicated by persistently positive anti-endomysial antibodies), and a thorough dietary review is essential. Other causes of persistent diarrhoea in patients believed to be on a strict gluten-free diet and in whom a malignancy has been excluded are detailed in *Table 2*.

A diagnosis of true non-responders or refractory coeliac disease can only be made if all the above conditions are excluded. Treatment for true non-responders includes steroids or other immunosuppressants, such as azathioprine or cyclosporin, failing which total parenteral nutrition is instituted in patients with severe weight loss, muscle wasting, multiple nutritional deficiencies or oedema secondary to hypoproteinemia. Recent studies suggest that many of these patients have a cryptic intestinal T-cell lymphoma or an adult form of autoimmune enteropathy and should therefore have T-cell receptor and monoclonal antibody studies performed and be screened for antienterocyte antibodies (Ryan and Kelleher, 2000).

FOLLOW-UP

Follow-up should be lifelong, ideally in a gastroenterology clinic. Body weight, full blood count, folate, calcium and alkaline phosphatase should be checked annually together with anti-endomysial antibodies to assess dietary compliance. Any new symptoms, such as weight loss, diarrhoea and abdominal pain, should be promptly reported and investigated. Screening of first-degree relatives should be discussed and the continuing need to strictly adhere to a gluten-free diet should be reinforced. Particular attention should be paid to pregnant patients who may develop asymptomatic nutritional deficiencies, as low folate levels have been associated with miscarriage and fetal neural tube defects.

COELIAC DISEASE IN THE NEW MILLENNIUM

The appreciation that coeliac disease is a global problem and not a disease confined to Europe has focussed the need for further research into the disease. Current areas of research include the search for the coeliac disease gene, developing a vaccine against coeliac disease, engineering gluten-free grains and the development of a non-invasive and reliable test for the diagnosis and follow-up of affected patients. HM

Conflict of interest: none.

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Useful addresses

The Coeliac Society
PO Box 220
High Wycombe
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Websites

www.coeliac.co.uk
www.celiaccenter.org
www.celiac.com

KEY POINTS

- Coeliac disease results from the ingestion of gluten in genetically susceptible individuals.
- Screening studies suggest that coeliac disease possibly affects 1 in 130–300 of the general population.
- Many patients have minimal symptoms, and delay in diagnosis is frequent.
- Antibody tests are useful for screening, but a small intestinal biopsy is essential for diagnosis.
- Treatment involves a strict gluten-free diet, which results in complete remission and which should be lifelong in view of the potential long-term complications.
- Coeliac disease remains underdiagnosed. Remember the aphorism 'think of coeliac disease and you will find it' (Holmes and Catassi, 2000).