Fortnightly review

Coeliac disease

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Coeliac disease is an inflammatory disease of the upper small intestine and results from gluten ingestion in genetically susceptible individuals.[1 2] Inflammation may lead to the malabsorption of several important nutrients. Clinical and mucosal recovery after institution of a gluten free diet is objective evidence that the enteropathy is gluten induced. In 1950, Dicke observed the central role of gluten in the pathogenesis of coeliac disease.[3] Coeliac disease is closely related to dermatitis herpetiformis.[4] In dermatitis herpetiformis, skin rash and a similar small intestinal enteropathy to that of coeliac disease are typically present, and both respond to withdrawal of gluten.

Summary points

- In coeliac disease, dietary gluten causes inflammation of the small intestine, which may affect absorption of important nutrients including iron, folic acid, calcium, and fat soluble vitamins
- Studies show coeliac disease to be a common disorder, possibly affecting 1 in 200 of the general population, the majority of patients being diagnosed in adulthood
- Many patients have minimal symptoms, and gastrointestinal symptoms are frequently absent
- Coeliac disease should be considered in a wide range of clinical situations including anaemia or osteoporosis and in patients with a range of associated disorders such as type 1 diabetes
- The diagnosis and screening for coeliac disease has been facilitated by testing for endomysial autoantibodies
- Treatment consists of permanent withdrawal of gluten from the diet, which results in complete remission

Methods

My review is based on the proceedings of regular international symposiums[5–7] and meetings[8] on coeliac disease, textbooks,[1 2] review articles,[9] and searches of Medline (250 articles were published in 1997 alone).

Symptoms and signs

A range of symptoms and signs may be associated with untreated coeliac disease, and these can be divided into intestinal features and those caused by malabsorption [1 2 9] (box 1). It should be emphasised, however, that many patients—especially those presenting in adulthood—have minimal or atypical symptoms.[10 11]

In infants less than 2 years of age, a more fulminant presentation of coeliac disease is likely, and chronic diarrhoea, failure to thrive, abdominal distension, and vomiting may occur.[12] This clinical presentation is now uncommon, and as paediatric patients tend to present at a later age (median 4 years), features such as loss of appetite and short stature may predominate.[13]

Intestinal symptoms may be absent in adults with coeliac disease, but in many clinically overt cases oral ulceration, dyspepsia, abdominal bloating, and diarrhoea may be present.[1 2 9] In some patients manifestations caused by malabsorption such as anaemia or osteoporosis may be found, whereas in others the predominant features may be of a disorder associated with coeliac disease—dermatitis herpetiformis is the classic example, with a typical pruritic vesicular rash.[4]

Epidemiology

A decade ago coeliac disease was considered a comparatively uncommon disorder, with prevalence rates of 1 in 1000 or lower quoted.[8 10] Several recent population studies, however, have shown a much higher prevalence, and it is now estimated that coeliac disease may affect 1 in 200 individuals.[14 15] The iceberg is a common model used to explain the epidemiology of coeliac disease (figure).[12] Accordingly, only a minority of individuals have clinically recognised disease, and this may explain the earlier inaccurately low prevalence figures. In contrast, the majority of patients have what is termed silent coeliac disease, which may remain undiagnosed because the condition has no symptoms.

The discovery that coeliac disease is a prevalent disorder can be attributed to the judicious use of serological screening tests, which measure antiendomysial and antigliadin antibodies.[14 15] Of these, the endomysial antibody test has advanced the diagnosis of coeliac disease owing to its specificity and sensitivity.[16 17] Further screening of populations should give information about the prevalence of coeliac disease worldwide.[11]

For example, on the basis of positive test results for endomysial antibodies, it is likely that coeliac disease is much more common in the United States than was previously thought.[18]

Coeliac disease can occur at any age, but in adults the peak incidence is in the fifth decade. Females are more commonly affected than males, and of those patients presenting during their fertile years, a female to male ratio of almost 3 to 1 has been observed.[17] Although coeliac disease is strongly linked with childhood, it is now well reported that coeliac disease in childhood has become increasingly uncommon.[11 12] Factors responsible for this change are much debated. The change may be partly explained by the exclusion of gluten from the diet of infants, a practise that became common in many countries in the 1970s. It is also hypothesised that children with the potential to develop coeliac disease may do so in later life after exposure to the necessary triggering factors.

Box 1—Symptoms (and related signs) of coeliac disease

- Infancy (< 2 years)

Diarrhoea (miserable, pale)
Abdominal distension (enlarged abdomen)
Failure to thrive (low weight, lack of fat, hair thinning)
Anorexia, vomiting
Psychomotor impairment (muscle wasting)

- Childhood

Diarrhoea or constipation
Anaemia
Loss of appetite (short stature, osteoporosis)

- Adulthood

Diarrhoea or constipation
Anaemia
Aphthous ulcers, sore tongue and mouth (mouth ulcers, glossitis, stomatitis)
Dyspepsia, abdominal pain, bloating (weight loss)
Fatigue, infertility, neuropsychiatric symptoms (anxiety, depression)
Bone pain (osteoporosis)
Weakness (myopathy, neuropathy)

Associated diseases

Many diseases have been associated with coeliac disease,[1 2] but as the high prevalence of coeliac disease is now known, it is possible that in many instances these are chance associations. Nonetheless, recent screening studies have shown an increased prevalence of coeliac disease in certain conditions such as type 1 diabetes[19] and autoimmune thyroid disease[20] (table). This may also be true of other autoimmune disorders—for example, primary biliary cirrhosis[21] and Sjögren's syndrome.[22] A common genetic background, in particular HLA type,[23] and similar immune mediated disease mechanisms, may underpin these associations. The sharing of a similar HLA haplotype[24] may partly explain the strong association between IgA deficiency and coeliac disease.[17 25] An increased prevalence has also been found in patients with osteoporosis.[26] In other instances, there are unexpected associations such as epilepsy[27] and various undefined neurological disorders.[28]

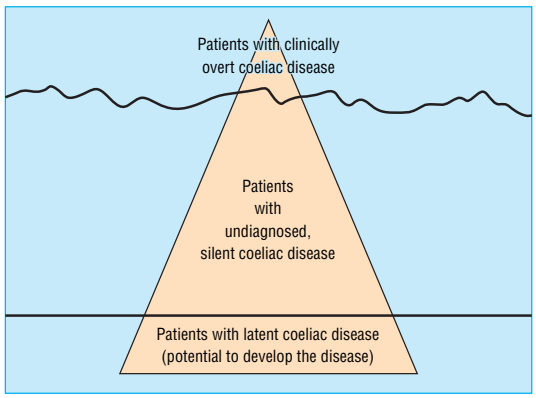
Diseases in adults associated with coeliac disease

Disease	Estimated frequency (%)
Type 1 diabetes[19]	2-7.8
Thyrotoxicosis[20 22]	5-5.8
IgA deficiency[17 25]	2-2.6
Sjögren's syndrome[22]	3.3
Primary biliary cirrhosis[21]	3
Osteoporosis[26]	3.3
Epilepsy[27]	2.3
Undefined neurological disorder[28]	17

Pathogenesis

As gluten acts as an essential factor in the pathogenesis of coeliac disease,[3] this raises the question of what makes a particular individual susceptible to gluten. Evidence suggests that hereditary factors play a significant role, and coeliac disease is diagnosed in around 10% of first degree relatives of an individual with coeliac disease.[10] Genetic factors alone, however, do not explain the development of coeliac disease, and it has been noted that the disease is concordant in only 60% to 70% of identical twins. Thus, additional factors such as infectious agents and hormonal status are likely to be involved. It has been speculated that in appropriate circumstances, after the intervention of some unknown environmental factors, ingestion of gluten establishes a chronic inflammatory reaction of the intestine in certain genetically predisposed individuals.[29]

Although the precise pathogenetic mechanisms in coeliac disease are unknown, T cells may play a central role. T cells may react with tissue transglutaminase (the principal component of the endomysium autoantigen),[30] and set in motion a series of inflammatory events that result in the characteristic coeliac mucosal lesion.



Iceberg model depicting prevalence of coeliac disease

Diagnosis

Histological identification of gluten sensitive enteropathy is the accepted basis for diagnosing coeliac disease.[1 2] In classic cases of coeliac disease, a characteristic inflammatory small intestinal lesion referred to as villous atrophy is found. In some patients, however, a less florid lesion is present,[31] and this can cause difficulties with diagnois.[17] Unequivocal evidence that the lesion is sensitive to withdrawal of gluten may require three small intestinal biopsies: before treatment, after withdrawal of gluten, and after challenge with gluten. Such a series of biopsies is rarely performed, and a single initial biopsy may be judged sufficient.

With the advent of the endomysial antibody test,[16] serological diagnosis of coeliac disease has come to the forefront. Endomysial antibodies are closely associated with gluten sensitive disease, and in an appropriate clinical setting coeliac disease can be diagnosed with 100%

Box 2—Management plan for treatment of coeliac disease

- Initiate a strict gluten free diet
- Monitor progress in a dedicated coeliac clinic
- Ensure regular consultation with a trained dietician
- Add supplements of deficient nutrients—for example, iron, folic acid, calcium
- Monitor dietary adherence by serial tests for antiendomysial and antigliadin antibodies
- Repeat an intestinal biopsy if clinical progress is suboptimal

specificity. As the assay is dependent on the detection of IgA antibodies, the endomysial antibody test is obviously negative in individuals deficient in IgA, but is also negative in a proportion of other patients; however, a sensitivity of 86% or greater has been observed.[17 32] Assays for antigliadin antibody can help in this situation, enabling almost all patients to be identified.[33]

It was recently reported that measurement of antitissue transglutaminase antibodies in an enzyme linked immunosorbent assay (ELISA) system might be an alternative and more objective method for detecting endomysial antibodies.[34 35] Early experience suggests, however, that a positive antitransglutaminase test is less specific for diagnosing coeliac disease than the traditional immunofluorescence endomysial antibody assay (personal observation).[34]

It could be argued that a positive test result for endomysial antibody, with an appropriate clinical response to withdrawal of gluten, is sufficient to diagnose coeliac disease. The combination of histology and endomysial antibody test results, however, provides complementary data and affords the most secure diagnostic information: this approach is likely to remain—for the present at least.

A further range of tests, such as D-xylose absorbtion, were previously used to help establish a diagnosis of coeliac disease, but these investigations are no longer required and are effectively redundant.

Treatment

Box 2 lists a management plan for the treatment of coeliac disease. Permanent withdrawal of gluten from the diet remains the current essential treatment. After commencement of a gluten free diet, the patient's progress should be monitored—preferably in a specialist coeliac clinic. Most patients show a rapid clinical response, with improvement of symptoms within weeks.[9] Histological improvement is slower, and complete mucosal recovery can take months or years. Although avoidance of products containing gluten is straightforward, the complex manufacture of modern processed food means that the ongoing advice of a trained dietician is required. Guidelines and food lists provided by lay coeliac societies are also invaluable. Adherence to a gluten free diet can be monitored by serial measurement of antigliadin or antiendomysial antibodies. A minority of patients do not respond to a gluten free diet, and the commonest explanation is continued ingestion of gluten (intentional or inadvertent). A repeat small intestinal biopsy is not necessary, although it may be performed when clinical response or adherence to a gluten free diet seems suboptimal.

In addition to wheat, barley, and rye cereal products, oats cereal is also traditionally excluded in a gluten free diet.[36] Two recent clinical studies have, however, provided strong evidence that oats do not damage the mucosa of patients with coeliac disease.[37 38] Recent guidelines from the UK Coeliac Society (December 1998) accepted that moderate amounts of oats can be consumed by most coeliac patients without risk. It is important to emphasise that the oats must be free of other contaminating cereals. Inclusion of oats in the diet provides a rich souce of fibre as well as several important nutrients. This may help alleviate the relative monotony of a strict gluten free diet.

Prognosis and complications

When a patient with coeliac disease is adequately treated with a strict gluten free diet, the prognosis is excellent and the patient can probably lead an otherwise normal life. Failure to implement a strict diet or failure to respond to dietary treatment may result in continuing symptoms and in the two major complications of osteoporosis[39] and malignancy.[40] A diagnosis of coeliac disease in a patient with osteoporosis provides an opportunity to introduce a specific management policy that can restore bone mineral density. All patients with osteoporosis should be screened for coeliac disease[26] by measurement of endomysial antibodies, and this would be a sensible, financially sound approach to offset long term morbidity.

The classic malignancy associated with coeliac disease is a lymphoma of the small intestine, called enteropathy associated T cell lymphoma.[40] Cancer of the small intestine, oesophagus, or pharynx are also well described malignancies associated with coeliac disease. In a carefully conducted longitudinal study, it was reported that a strict gluten free diet protected against these malignancies.[40] This protective effect (and protection against osteoporosis) remains the strongest argument for total withdrawal of gluten from the diet of patients sensitive to gluten. However, the exact risk that such patients are exposed to requires further evaluation, particularly the large number of undiagnosed cases with silent coeliac disease. This issue is currently under investigation.

In conclusion, coeliac disease is a common, underdiagnosed disorder,[41] with significant morbidity and mortality. A greater awareness of this disorder should be possible owing to the availability of a specific screening blood test and a highly effective dietary treatment.

This review is dedicated to the late Eoin Denis Feighery who shared my interest in coeliac disease. I thank Dr John Jackson and Professor Donald Weir, and Ms Teresa Shaw for secretarial assistance.

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Lesson of the week

Contrast enhanced computed tomography in the early diagnosis of cerebral abscess

Michael Owen Fitzpatrick, Peter Gan

Despite advances in the management of cerebral abscess, this condition is still associated with appreciable morbidity and mortality. The key to successful treatment is early diagnosis, but this requires a high index of clinical suspicion and the correct choice of investigations. Contrast enhanced computed tomography is the best investigation since non-contrast computed tomography does not identify all cerebral abscesses. To highlight this, we report two patients in whom the diagnosis was delayed because of failure to perform a contrast enhanced computed tomogram of the brain, and in whom delay may have resulted in a less favourable neurological outcome.

Case reports

Case 1

A 54 year old man presented to a district general hospital after a single grand mal seizure. Clinical examination showed a right hemiparesis and non-contrast computed tomography showed an area of low attenuation in the left temporal lobe which was reported as a temporal lobe infarct (figure, A). The patient had no further seizures, made a good recovery, and was discharged home 4 days after admission. Two weeks later he was readmitted because he had become confused. Repeat computed tomography of the brain showed that the area of low attenuation area was more extensive and there was an associated mass effect. These findings were reported as an established infarct. The man became less confused after a few days and was discharged home. Three days later he was readmitted to hospital in a coma. He was feverish (temperature 37.5°C), and his white cell count was 13.9×10^9/l. Contrast enhanced computed tomography showed a ring enhancing lesion in the right temporal lobe with appreciable midline shift (figure, B). The diagnosis of a brain abscess was made.

Case 2

A 50 year old woman presented with a short history of headache and numbness of her left hand. When she was first examined her level of consciousness was normal,

If a stroke is not straightforward, ask for a contrast enhanced computed tomogram

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