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Conference on 'Malnutrition matters'

Symposium 1: Joint BAPEN and British Society of Gastroenterology Symposium on 'Coeliac disease: basics and controversies' Coeliac disease in the twenty-first century

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Coeliac disease (CD), traditionally perceived as a rare childhood condition presenting with malabsorption, is instead an autoimmune multisystem disorder usually presenting in adulthood, affecting $\geqslant 1\%$ of the population and linked to the genetic expression of human leucocyte antigens (HLA) DQ2 and DQ8. Presentation occurs most often in the 40–60 years age-group, but potentially at any age. Symptoms attributable to the gut or to malabsorption may be mild, non-specific or absent; under one-third of patients have diarrhoea and almost half are overweight. Histological diagnosis no longer requires small intestine villous atrophy. The Marsh classification recognizes increased intraepithelial lymphocytes and crypt hyperplasia with intact villi as part of the gluten enteropathy spectrum, while some individuals have more subtle abnormalities identified only on electron microscopy. Serological testing for CD autoantibodies (to endomysium and tissue transglutaminase) has revolutionized diagnosis, shifting the process towards primary care. However, a substantial number of patients with CD are seronegative, particularly those without villous atrophy. The autoantibody to endomysium may be produced before histological change. The immune response to transglutaminase is crucial to the disease process. An exciting new development is the link between antibodies to organ-specific transglutaminases and clinical presentation; transglutaminases 2 (gut), 3 (skin) and 6 (nervous system). Negative testing for CD does not preclude its development later and HLA testing may allow 'once and for all' exclusion. In conclusion, an increasing proportion of patients with CD do not meet the 'classic' picture of malabsorption, positive serological testing and villous atrophy. Insisting on all these criteria for diagnosis will result in under diagnosis.

Coeliac disease: Diagnosis: Enteropathy: Autoantibodies

Coeliac disease (CD) is an autoimmune disease triggered in genetically-susceptible individuals by the ingestion of the gluten proteins of wheat, barley and rye. There is a strong association with other autoimmune disorders and, genetically, with the human leucocyte antigen (HLA) DQ2 and DQ8 alleles. The autoimmune processes of CD are directed against tissue transglutaminase (tTG) 2, resulting in the formation of autoantibodies to tTG (tTGA) and endomysium (EmA), which can be detected in the serum. Villous atrophy (VA) and an excess of lymphocytes are typical histological findings in the proximal small intestine (duodenum, jejunum). The present review covers the epidemiology, clinical presentations and diagnosis of CD with a particular focus on recent literature.

Pathogenesis of coeliac disease

CD shares with other autoimmune disorders a close association with HLA-linked genes; >90% of patients with CD are DQ2 positive, with most of the rest carrying DQ8 alleles[1]. Peptide sequences of dietary gluten, which are resistant to protease activity in the gut, are deamidated by tTG[2]. Deamidated gluten peptides form complexes with HLA-DQ and trigger a T-cell-mediated inflammatory

Abbreviations: CD, coeliac disease; EmA, endomysium antibodies; HLA, human leucocyte antigen; tTG, tissue tranglutaminase; tTGA, tTG antibodies; VA, villous atrophy.

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response[3]. While this response has direct effects on the small bowel mucosa, CD is a multisystem disorder affecting potentially any organ system and there is evidence that autoantibodies directed against tTG as part of the process have consequences elsewhere in the body.

Epidemiology

Failed and delayed diagnosis of CD used to be common, as clinicians failed to recognize the various manifestations of CD and their potential to commence at any age[4–6].

Far from being a rare condition, population-screening studies indicate not only that CD affects approximately 1% of many populations with European ancestry, including those in the Americas and Australasia[7], but also that it is as common in the Middle East[8,9] and the Indian subcontinent[10]. Most patients present for the first time with symptoms in adulthood, with peak onset of symptoms in the 40–60 years age-group[11]. Onset of symptoms and diagnosis are often in later life; in one Italian study 4% of patients were diagnosed after the age of 65 years[6].

Clinical presentations

Potential clinical presentations can be categorized into three main groups, although some symptoms have more than one basis:

1. malabsorption, e.g. diarrhoea, abdominal pain, flatus–flatulence, weight loss, anaemia, osteomalacia, osteoporosis;
2. gut dysmotility, e.g. reflux, dysphagia, dyspepsia, constipation;
3. autoimmunity, e.g. dermatitis herpetiformis, neuropathy, ataxia.

BMI and gastrointestinal symptoms

While the patient with CD was traditionally considered to be underweight, with symptoms attributable to malabsorption such as diarrhoea, flatus and abdominal distension, recent studies report that 28–39% of patients are overweight (BMI $\geqslant$25 kg/m^2) at presentation[12–14]. In the author's own experience fewer than one-third of patients report diarrhoea as a presenting symptom[11]. In a US study the percentage of patients diagnosed with CD who presented with diarrhoea fell from 73% pre-1993 to 43% after 1993[15]. Traditionally, some patients with CD were wrongly diagnosed as having irritable bowel syndrome; new guidelines from the UK National Institute for Health and Clinical Excellence[16] recommend that coeliac serology should be checked in all patients suspected of having irritable bowel syndrome. The possibility of dual pathology should be considered in patients with CD who do present with diarrhoea. There is an association between CD and inflammatory bowel disease[17] and the author's own approach is to perform colonoscopy in patients with CD presenting with altered bowel habit after the age of 40 years to exclude coincidental colon neoplasia[18]. Diarrhoea that does not rapidly respond to gluten exclusion should prompt a search for small bowel neoplasia and ulcerative jejunitis complicating CD[19]. There are also links with exocrine pancreatic insufficiency, which may be easily detected using faecal elastase assays[20], with small intestinal bacterial overgrowth[21] and with microscopic colitis[22].

Many patients with CD present with symptoms more typically associated with the upper gastrointestinal tract, including reflux, nausea, dysphagia and epigastric pain. These symptoms are related in part to gut dysmotility, which is well documented in CD, although the mechanism is uncertain[23]. The constipation that is paradoxically seen in some patients with CD is probably explained on the same basis. Patients with these symptoms are more likely to undergo upper gastrointestinal endoscopy as a first-line investigation. While duodenal biopsy as a routine at every endoscopy is not cost effective, it should be performed in patients having endoscopy for anaemia who have a family history of CD and considered for those with dyspeptic symptoms that have not responded to conventional acid suppressants. A proportion of patients with VA have endoscopic abnormalities in the duodenum (scalloped folds; fold loss; mosaic, grooved or nodular mucosa; erosions; visible vessels), which should prompt biopsy if seen[24].

Anaemia and B-vitamin deficiency

Fe deficiency

Fe, whether derived from animal (haem) or plant sources, is absorbed in the duodenum and jejunum and Fe deficiency is to be expected as a result of the proximal enteropathy of CD. In the author's experience approximately one-third of new patients present with Fe-deficiency anaemia without gastrointestinal symptoms[11], while Fe deficiency has been reported in 33% of men and 19% of women at diagnosis[25]. The Fe-deficiency anaemia of CD often does not respond to supplements until a gluten-free diet is started. When bleeding sources are excluded by upper gastrointestinal endoscopy and colon investigation, CD is confirmed in 10% of all patients with Fe-deficiency anaemia[26] and in 20% of individuals identified as having Fe deficiency by pre-blood-donation screening[27].

Folate deficiency

Like Fe, folic acid is absorbed in the proximal small bowel and deficiency in patients with CD is common, affecting 12% of a recent US study cohort[25]. Confusion may be caused when Fe and folate deficiency co-exist, resulting in normalization of the mean cell volume. An increase in erythrocyte distribution width as the result of a dimorphic population of erythrocytes allows differentiation of both mixed Fe and folate deficiency and Fe and vitamin B_{12} deficiency from the anaemia of chronic disease. It has been proposed that an increased erythrocyte distribution width should prompt testing for CD[28].

Vitamin B_{12} deficiency

Although the primary site of vitamin B_{12} absorption is the terminal ileum, vitamin B_{12} deficiency is common in CD,

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affecting 5–41 % of adult patients[25,29,30]. The reduction in serum vitamin B_{12} level associated with CD is much less than that typically seen in autoimmune gastritis (true pernicious anaemia).

Homocysteine

Folic acid and vitamin B_{12}, along with vitamin B_6 and riboflavin, are needed for the metabolism of homocysteine, which is widely considered to be a risk factor for heart disease and stroke. Higher levels of homocysteine have been found in untreated patients with CD compared with healthy controls, with normalization after recovery of VA[31]. Raised homocysteine may account for the prevalence of stroke and cardiac disease in patients with CD, which is comparable with rates in controls, despite generally lower cholesterol levels[13].

Other haematological problems

Hyposplenism is well recognized as a complication of CD. It may be identified by the presence of Howell-Jolly bodies, acanthocytes and target cells on blood film analysis, raised platelet counts and 'pitted' erythrocytes[32]. A recent English study has reported a twofold risk of pneumococcal infection in patients with CD[33]. Accordingly, screening for hyposplenism in CD seems appropriate, with relevant vaccinations where they are not routinely administered. Dapsone, used in the management of dermatitis herpetiformis, is associated with methaemoglobinaemia, haemolytic anaemia and neutropenia.

Liver disease

A substantial minority of patients with CD have raised serum levels of aspartate and alanine transaminase on liver function testing, which settle after gluten exclusion[34–36]. Serological testing for CD should be part of the initial investigation of raised serum transaminases. Where liver biopsies have been performed in this situation they show changes of non-specific hepatitis and specific liver investigation is usually not required. While raised serum transaminases are usually an incidental finding, there have been patients with severe liver disease requiring transplantation in whom CD has been identified and appropriate treatment has reversed liver failure[37].

However, it is important to differentiate this finding from specific autoimmune liver diseases that have been linked with CD. Patients with primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis all have an increased prevalence of CD[38]. Diagnostic confusion may arise from raised serum tTGA levels in primary liver disease with no evidence of CD. tTGA assays may give a false positive reaction in liver fibrosis[39].

Bone and joint disease

Traditionally, CD presenting with overt malabsorption was associated with osteomalacia and rickets, manifest as bone pain and reduced serum Ca and phosphate. This disorder is now seldom seen and the widespread availability of dual-energy X-ray absorptiometry scanning has shown that osteoporosis–osteopenia is by far the commonest bone disorder of CD, affecting 20–50 % of patients at diagnosis[40–42]. Aetiological factors include Ca and vitamin D malabsorption and secondary hyperparathyroidism, but serum bone-specific autoantibodies have been described[43].

In most cases osteoporosis is asymptomatic and picked up by dual-energy X-ray absorptiometry screening. More important than the prevalence of osteoporosis is its clinical impact, and recent case–control studies suggest that fracture risk remains low in absolute terms, ranging from no risk to only a twofold increase compared with controls[44–46]. Guidelines produced for the British Society of Gastroenterology recommend that all adults with CD should have dual-energy X-ray absorptiometry at diagnosis[47], but the authors of the guidelines have recently questioned this approach[48]. The merit of screening patients with osteoporosis for CD is uncertain. There is no increase in CD prevalence among post-menopausal women[49], although the yield in other groups may be higher. Where reduced bone density is identified in CD there is improvement with gluten exclusion[50,51].

Arthritis and joint pain are well described in CD[52]. Of specific rheumatological disorders only Sjogren's syndrome, which shares DQ2 and DQ8 haplotypes, appears to be associated with CD, with a prevalence of 5–15 % among patients with Sjogren's syndrome[53,54]. The finding of tTGA in patients with other forms of arthritis may be a non-specific finding[55].

Skin disease

Dermatitis herpetiformis, an intensely-itchy blistering rash characteristically affecting the buttocks, elbows and knees is the typical skin lesion of CD and was the first and best-described extraintestinal manifestation of gluten sensitivity. Clinical characteristics of 264 US patients have recently been published[56], showing an excess of male patients in contrast to the female preponderance in most CD series. Patients presenting with dermatitis herpetiformis appear to have a lower risk of complications such as osteoporosis[57]. Dapsone is highly effective in achieving skin remission but has no effect on other organ involvement[58]. Gluten exclusion may take months to control the rash, but will allow Dapsone withdrawal within 18 months in most cases[58].

Infertility and miscarriage

For some years a link between CD and infertility or recurrent miscarriage has been reported[59], but studies were small, making interpretation difficult. In a recent large case–control study that used primary-care data for >1500 women with CD and 7700 matched controls it was found that while crude fertility rates are almost identical, age-specific fertility rates show that women with CD have lower fertility when younger but higher fertility when older compared with women without CD[60]. This age-related

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increase in relative fertility is independent of treatment for CD. Furthermore, risks of caesarean section (OR 1·33) and miscarriage (rate ratio 1·31) are moderately higher in women with CD, but risks of assisted birth, breech birth, pre-eclampsia, postpartum haemorrhage, ectopic pregnancy, stillbirth and termination are similar. However, the effects of socio-economic or educational advantage rather than a true disease effect could not be excluded. A comparison of the outcomes of children of mothers with CD before and after diagnosis and treatment has shown that rates of intrauterine growth retardation, low birth weight, pre-term birth and caesarean section are higher in the before diagnosis and treatment group, suggesting a beneficial effect of gluten exclusion[61].

Neurological disease

Neurological manifestations of CD are extensively described in the literature, and again may be the primary presentation with little or no gastrointestinal symptomatology[62]. Some, but not all, studies report an excess of epilepsy among patients with CD and vice versa[63–65]. A specific syndrome of bilateral occipital cerebral calcification, partial seizures and CD is rare, with <200 patients reported in the literature and geographically localized to Italy, Spain and Argentina[66]. Better-established associations are with peripheral neuropathy[67,68] and cerebellar ataxia[68–70]. CD has been found in 4% of ninety migraine sufferers compared with 0·4% of 236 controls[71]. Conversely, the prevalence of headache in 176 patients with CD has been reported to be 46% compared with 29% for controls[72]. Both studies indicate that gluten exclusion brings about an improvement.

Neurological problems were traditionally assumed to be a result of malabsorption, but nutritional deficiencies have not been consistently demonstrated and neurological symptoms do not respond to supplementation[73]. Specific autoantibodies directed at components of the nervous system have been described in patients with CD[74,75].

An English study has suggested that neurological disease as a result of gluten sensitivity may exist without enteropathy[76]. Patients thus affected may lack tTGA and EmA and have normal duodenal biopsies by conventional criteria. These findings question the reliance on small bowel histology to confirm a diagnosis of CD.

Diagnosis of coeliac disease

The most important step in diagnosis is to think of the possibility, which requires awareness of the many possible presentations of CD. In addition, suspicion should be higher where there is a family history of CD and in patients with a number of autoimmune conditions that are associated through HLA with an increased prevalence of CD; as well as liver disease and Sjogren's syndrome already mentioned, these conditions include type 1 diabetes mellitus[77], autoimmune thyroid disease[78] and Addison's disease[79]. There is an increased prevalence of CD in Down syndrome[80]. Upper gastrointestinal endoscopy, for whatever indication, in these patients should include duodenal biopsies as a matter of routine, as well as in patients with anaemia and with visible stigmata of VA in the duodenum[24]. It is important that an adequate gluten intake is maintained until serology and biopsies are obtained. Empirical reduction in gluten intake, on the advice of family, friends, alternative practitioners and even physicians may result not only in false negative serology but also normalization of duodenal histology.

Serological tests

Serological testing, using EmA and tTGA, has revolutionized the diagnosis of CD by allowing investigation by non-gastroenterologists who are more likely to observe its manifestations beyond the gut. As a result, the majority of cases of CD in the author's practice are identified initially by general practitioners[11]. Detection of EmA requires an operator with a microscope to check for antibody fluorescence, making the test labour-intensive and subjective and providing at best a semi-quantitative result. In contrast, tTGA assays typically use ELISA, which can provide a quantitative and non-operator-dependent result by automated spectrophotometry. Recently, kits have become commercially available that allow rapid near-patient testing for tTGA. These products include the Biocard (Ani Biotech Oy, Vantaa, Finland), which measures IgA human tTGA on a finger-prick blood droplet, and the Stick CD1 (Operon SA, Saragoza, Spain), which uses serum to test for IgG and IgA human tTGA. Their performance is similar to lab-based assays and the ease of use of the Biocard offers the opportunity for testing in the community by paramedical staff such as district nurses[81].

Sensitivity of serological tests

Research data to date in relation to the performance of lab-based IgA EmA and tTGA for CD has been summarized recently[82]. While some studies report sensitivity and specificity approaching 100%, these studies are often performed in research facilities with a much higher CD:non-CD sera than that seen in clinical practice, which will tend to improve performance. A further problem is that the criteria used for diagnosis of CD vary from study to study, with some excluding milder grades of VA and Marsh I and II lesions (for details of the Marsh classification of lesions, see later and Marsh[83]). Research from routine clinical practice indicates that serology has 80–90% sensitivity[84,85] for Marsh III histology. Both EmA and tTGA have lower sensitivities for milder degrees of VA[86,87]. Patients with non-VA gluten sensitivity (Marsh I, Marsh II) are more likely to test negative for tTGA and EmA[88]. Approximately 2·5% of patients with CD have selective IgA deficiency, representing a tenfold increase in prevalence over the general population[89]. These patients cannot produce IgA EmA and tTGA. While some centres measure total IgA routinely with coeliac antibodies, quantitative tests such as tTGA will show very low or zero levels in cases of selective IgA deficiency[90] and this situation should prompt IgG class tTGA and EmA measurements. Antigliadin antibody assays, previously widely used in diagnosis, are now considered to be obsolete in most centres because of poor sensitivity and specificity[82].

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Recently, serological testing for antibodies to deamidated antigliadin has been shown to have similar performance to tTGA assays, but further studies are needed[91].

False positive tissue transglutaminase antibodies

tTGA may be found in liver disease[39], arthritis[55] and end-stage heart failure[92] without evidence of CD. These false positive results may be a result of increased non-specific tTG activity in inflammation occurring in any organ system. A high percentage of children with tTGA will seroconvert without dietary restriction[93], suggesting a temporary phenomenon in some cases. Currently, there are no data as to whether patients with high tTGA and no evidence of CD are at greater risk of its development later.

No such thing as false positive endomysium antibodies?

Approximately 10% of patients with EmA do not have VA on duodenal biopsy[94]. However, some of these patients have Marsh I lesions, and of the remainder most will develop VA on follow-up biopsy or will respond symptomatically to a trial of dietary gluten exclusion[95,96]. Furthermore, electron microscopy studies of duodenal biopsies from patients who are EmA-positive but with no abnormality under light microscopy[97] show reductions in microvilli height, reduction in microvilli density and branching and enterocyte damage; again, progression to VA is observed during follow-up. It is likely that EmA positivity can precede the development of histological lesions and should be considered as a true manifestation of gluten sensitivity rather than a false positive finding.

Organ-specific transglutaminase antibodies

Recent work suggests that gluten sensitivity may be associated with autoantibodies against organ-specific transglutaminases. While the autoantigen in patients with coeliac enteropathy is transglutaminase 2, sera from patients with dermatitis herpetiformis react in addition to transglutaminase 3, which is epidermal in origin[98]. Similarly, sera from patients with gluten-related cerebellar ataxia have activity against the neuronal isoenzyme transglutaminase 6[99]. If these autoantibodies are shown to be specific for gluten-related disease, they may have value in diagnosis, particularly where intestinal involvement is minimal or undetectable.

Duodenal histology in coeliac disease

The demonstration of characteristic inflammatory and atrophic abnormalities of the proximal small intestine in duodenal biopsies remains central to the diagnosis of CD, both to support the diagnosis where serology is positive and to confirm the diagnosis in patients with characteristics suggesting CD despite negative EmA or tTGA. Traditionally, VA was required to make a diagnosis of CD, but in 1992 a spectrum of changes consistent with gluten enteropathy were described by Marsh[83]. In the Marsh I lesion the villi are intact but infiltrated by intraepithelial lymphocytes (>30/100 enterocytes), in Marsh II this lymphocytosis is accompanied by hyperplasia of the crypts, while the 'classic' CD lesion, showing these changes plus atrophy of the villi, is termed Marsh III[100]. Milder degrees of gluten enteropathy are clinically significant. Relatives of patients with CD who have Marsh I lesions identified through family screening are more likely to have symptoms, anaemia and reduced bone density than those with normal histology[101]. However, the characteristic finding of Marsh I enteropathy, intraepithelial lymphocytosis, poses a greater problem in relation to specificity for gluten enteropathy, as it is seen in 1–2% of all duodenal biopsy samples[102,103], and may be a result of other gut pathologies, including other dietary protein intolerance, parasites, *Helicobacter pylori* gastritis, bacterial overgrowth and inflammatory bowel disease[104]. Support for gluten sensitivity is provided by family history of CD, by positive serology in a minority of cases[94,95] and by determination of HLA-DQ2 and -DQ8 status. In the absence of these factors and with no alternative diagnosis a trial of gluten exclusion may be warranted.

The recent description of 'microenteropathy', with changes associated with gluten sensitivity visible only under electron microscopy[97], suggests that the spectrum of gluten-sensitive enteropathy extends even further than Marsh I.

Conclusions

CD is a common autoimmune disorder affecting multiple organ systems. Patients may present at any age and with wide-ranging symptoms. Serological testing using EmA and tTGA has revolutionized diagnosis, while duodenal biopsy remains a mainstay of baseline investigation, although histological changes may be more subtle than VA. However, there needs to be awareness of the limitations of serological testing with a well-documented false negative rate and, in the case of tTGA, false positives, while there is increasing evidence of gluten-sensitive disease with minimal or not readily demonstrable gut involvement. Autoantibodies against organ-specific transglutaminases may have a role to play in diagnosis. The only certainty is the association with HLA-DQ2 and -DQ8. In the future, diagnosis of CD may be made by weighing up various factors (clinical, serological and histological), with none individually necessary for the diagnosis.

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