

TITLE:**PATTERNS AND PRESENTATIONS OF ADULT COELIAC DISEASE IN A RURAL SETTING****AUTHORS**

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CONFLICT OF INTEREST

None

PATTERNS AND PRESENTATIONS OF ADULT COELIAC DISEASE IN A RURAL SETTING

Abstract

Background In recent years there has been a noticeable change in the patterns and presenting symptoms of coeliac disease. This may lead to delayed diagnosis and treatment and hence increased development of complications.

Aim The aim of this audit was investigate the presenting complaints of patients diagnosed with Coeliac Disease. In addition, the prevalence of associated conditions in coeliac patients.

Methods Observational retrospective cross-sectional study using the medical notes from the time of diagnosis of 32 adult patients attending the specialist coeliac clinic.

Results The main presenting complaint was anaemia at (21 patients, 66%). Less than half of the patients had any of the classical symptoms of coeliac disease and 8 patients (25%) had no classical symptoms at all. Biopsy was 97% sensitive, with Anti-gliadin antibodies, Anti-endomysial antibody and anti-tissue transglutaminase showing 75%, 68% and 90% sensitivity respectively. In combination, serology results were 100% sensitive. Fifty nine percent had developed osteoporosis or osteopenia. There were no malignant complications among the group.

Conclusion The majority of patients did not present with diarrhoea and weight loss, the commonest presentation being with anaemia.

Key Words

Coeliac disease, diarrhoea, anaemia

PATTERNS AND PRESENTATIONS OF ADULT COELIAC DISEASE IN A RURAL SETTING

Introduction

Coeliac disease is a permanent intolerance to ingested gluten, a protein found mainly in wheat, which produces characteristic intestinal lesions in susceptible individuals (1, 2, 3). The screening prevalence rates in Caucasians in Europe, North and South America, Australia and the Middle East reach 1 in 100, supporting the notion that coeliac disease is of clinical importance (4, 5, 6).

In the early 1980s, researchers began to show that presentations of the disease were changing (7). Often presenting with symptoms not previously considered to be characteristic of the disease (3, 9, 10). While most gastroenterologists appreciate the broader spectrum of the disease, and its increasing prevalence, most general practitioners still think of coeliac disease as a rare condition presenting with diarrhoea and weight loss, with or without abdominal pain (9). There is concern that many cases of the disease are being overlooked due to the failure of doctors to consider it in the initial differential diagnosis of patients complaining of non-classical symptoms (8), which now form the majority of the clinical spectrum of the disease.

Hence early diagnosis of coeliac disease is important. Many cases are diagnosed only when they present with complications, although malignancy as a complication is rare (11, 12). While the role of the gluten free diet in reducing complications is not irrevocably proven, it does appear to be protective, particularly against non-Hodgkin's

lymphoma (13), the most commonly associated malignant complication (11), and disorders of bone metabolism (14, 15, 16).

Methods

Thirty-two patients attending three consecutive clinics were randomly selected. They were attending a specialist multidisciplinary adult coeliac clinic run by a specialist physician and a specialist dietitian in a district general hospital in rural South Wales to which local patients with coeliac disease are referred. The following were determined - Age at diagnosis, Sex, Time delay between onset of symptoms and diagnosis, Comorbidities, Presenting complaint(s), Family history of coeliac disease or autoimmune disorders, Haematology at diagnosis, Full blood count, Red cell folate, Ferritin, Serum B12, Serology at diagnosis (Elisa technique), Anti-gliadin antibodies (IgA), Endomysial antibodies (IgA), Anti-transglutaminase antibodies (IgA), Biopsy result at diagnosis (Marsh Classification), Source and reason for referral, Result of DEXA scan (first scan following diagnosis) and Presence of dermatitis herpetiformis.

When relevant serology tests were not performed at the time of diagnosis, these cases were excluded. Four (13%) ferritin, 5 (16%) folate and 6 (19%) B12 values were unobtainable. Twelve (38%) anti-gliadin antibody values, 10 (31%) anti-endomysial antibody 4 (13%) anti-tTG results were not available, and these were excluded as well.

Where patients were being treated for anaemia prior to diagnosis with coeliac disease, haematological values before commencement of iron, B12 or folate replacement therapy were taken, as medication would have restored these values thus creating a falsely low rate of coeliac patients with anaemia at time of diagnosis.

Results

The ratio of male:female cases was 1:1.5 and the mean age at diagnosis was 53.2 (range 23-86). There were two peaks in diagnosis, in the 4th and 6th decades (figure 1). The time from onset of symptoms to diagnosis with coeliac disease ranged from 1 week to 25 years and with mean 71 months. There was no correlation between age at diagnosis and time elapsed between onset of symptoms and diagnosis in this study ($r=0.18, p>0.05$), thus the possibility of diagnostic delay is effectively ruled out.

Comorbidities

A number of patients had co-existing autoimmune disease. Amongst patients with thyroid disease, 57% (18 patients) had hypothyroidism and 29% (9 patients) were thyrotoxic while the remaining patient had thyroiditis. Eighty three percent of the cases with affective disorder had depression. Fifty seven percent of arthritis cases were not degenerative in nature.

No patients in the study had type 1 diabetes mellitus or Sjögren's syndrome. One patient had inflammatory bowel disease.

Fourteen percent of cases were IgA deficient. The prevalence of pernicious anaemia was 9% and primary biliary cirrhosis 6%. Atopic disease was present in 6% of cases and one patient had sarcoidosis.

Presenting Complaints

The most common presenting complaints are listed in table 2. Less than 50% patients had each of the “classical” symptoms of coeliac disease, with the majority having presented with iron deficiency anaemia. Sixty eight percent were found to have low iron stores (ferritin <20ng/l) at the time of diagnosis. 50% had a reduced haemoglobin, 35% a low mean corpuscular volume and 45% a low red blood cell count. Mean cell volume is complicated by 57% cases having low folate or low B12. 13% patients had high MCV at time of diagnosis.

25% (8) cases presented with no “classical” symptoms, all 8 subjects were found to have iron-deficiency anaemia. Only one case (3%) had dermatitis herpetiformis although 25% cases suffered with skin conditions “diagnosed” as follicular rash, eczema, seborrheic dermatitis, lichen planus or pruritis of unknown aetiology.

Referral Source

Thirty eight percent of cases were referred by the general practitioner, while 22% were referred by a haematologist. 9% were referred by surgeons and 9% were diagnosed following emergency admission to hospital with acute episodes of abdominal pain, diarrhoea or vomiting. The remaining cases were referred by general hospital physicians and care of the elderly specialists (chronic anaemia), gynaecologist (abdominal pain), dermatologist (skin rash) and rheumatologist (iron-deficiency anaemia) (figure 2).

Family History

Positive family history (coeliac disease in a first degree relative) was found in 3 cases. 16% had a family history of other autoimmune diseases.

Serology

Of all the patients, seventy five percent of patients were found to have positive anti-gliadin antibodies (AGA) at diagnosis and 68% had positive endomysial antibodies (EMA) while 91% patients were positive for EMA, AGA or both (95% confidence interval 79.3-102.7%). 90% had positive anti-tTG (95% CI 71.4-108.5%). Only eight cases had all 3 antibodies tested at the time of diagnosis, owing mostly to the diagnosis of most subjects before the tests became routinely available.

Histology

The changes in one case only (3%) showed an increase in the intraepithelial lymphocytes. The most common finding (47%) was partial villous atrophy; 22% had subtotal and 16% partial-subtotal villous atrophy, while only 13% patients demonstrated total villous atrophy (figure 3).

Complications

The only complication found among cases was osteoporosis, which was present in 28%, with 31% cases being osteopenic (osteoporosis = T score < -2.5, osteopenia = T score < -1.0). DEXA scans were carried out a mean of 124.7 months after onset of symptoms (but 43.4 months following diagnosis). There was no correlation between T score and the length of time the DEXA scan was performed following the onset of

symptoms (L-spine: $r = -0.64$, $p = 0.757$; hip: $r = -0.108$, $p = 0.601$), or between T score and the length of time elapsed following diagnosis (L-spine $r = -0.320$, $p = 0.110$; hip $r = -0.0279$, $p = 0.167$).

There were four cases of malignancy in the group, of these two cases were of basal cell carcinoma, one of melanoma and one of breast cancer. There were no cases of lymphoma, adenocarcinoma of the small intestine or oesophageal or pharyngeal carcinoma.

Discussion

Coeliac disease is more common in women than men (18, 19) and the cases presented in the study concur with this, with a male:female ratio of 1:1.5. It is known that women actively seek health advice more readily than men (7, 21) and the high relative incidence in women may thus be a result of this behaviour.

It is also possible that the higher incidence in women could be due to the increased nutritional demands of women during the reproductive years (7). This is supported by the finding that in children the ratio of boys: girls with coeliac disease nears one (7, 20).

The mean age at diagnosis in this study was 53.2, with peaks in the 4th and 6th decades. This concurs with the findings of other studies (8, 10). No cases were diagnosed in childhood because the cases were taken from an adult coeliac disease clinic.

Thirty eight percent of cases in this study were referred directly by the GP. Twenty two percent of patients were referred directly by a haematologist, reflecting the high incidence of anaemia among the group. Many patients who eventually underwent endoscopy to find a cause of their anaemia underwent both colonoscopy and gastroscopy to exclude malignancy.

Unnecessary delays in diagnosis predispose patients to developing complications (14-16). It has been shown that adherence to the gluten-free diet is protective against

malignancy in coeliac disease (13). A cohort study of 210 coeliac patients who followed a gluten-free diet for a mean of 18.5 years, found that the risk of developing cancer is not significantly increased in those who followed a gluten free diet for five years or more when compared with the normal population (13). They found however that those taking a reduced gluten or normal diet had an increased risk of developing cancer, especially lymphomas and cancers of the mouth, pharynx and oesophagus.

Disorders of calcium and bone metabolism were the most prevalent complications. Thirty one percent were osteopenic while 28% had osteoporosis. One patient had secondary hyperparathyroidism. Delayed diagnosis and hence delayed treatment causes increased chance of development of osteopenia or osteoporosis (14). There is evidence also to show that compliance with a gluten-free diet increases the bone mineral density of osteopenic coeliac patients (15, 16). Other complications such as neurological disorders and infertility were not found in any patients in this study.

The most common presenting complaint was iron-deficiency anaemia. The next most common complaint was of abdominal pain or discomfort, which was often non-specific and longstanding. Patients for whom abdominal pain was the primary symptom had often undergone prolonged testing under other specialties such as gynaecology or surgery before being referred to the coeliac clinic. 6 of the 13 patients with abdominal pain or discomfort had had a chronic undiagnosed anaemia for years before developing the gastrointestinal symptoms which eventually led to their diagnosis.

Zipser et al. (10), who conducted a similar study in the USA found fatigue to be the most common presenting symptom, with 82% patients complaining of this. In contrast, fatigue featured relatively low down on the list of the cases studied here, with only 31% of case notes documenting this problem. A comparison between the findings of this study and those by Zipser et al. are shown in table 1.

Although 57% cases had low folate or low B12 at the time of diagnosis, only 13% had a raised MCV. Of those with a low folate or B12 but no increased MCV, 91% had a low ferritin, which would account for a normal or lower MCV than expected resulting in mixed deficiency anaemia.

Family history was taken as positive if a first degree relative was diagnosed with coeliac disease. Three cases met these criteria. Around 10% of first degree relatives are diagnosed with coeliac disease (8). However, first degree relatives were not screened and those might have undiagnosed subclinical or silent disease.

Sixteen percent of patients had a first degree relative with an autoimmune disorder. The prevalence of autoimmune disorders among coeliac relatives has been shown to be higher than among the general population. It was also shown that those relatives with an autoimmune disease were more likely to have silent than symptomatic coeliac disease (24).

The most common comorbidity in the cases presented here was thyroid disease (22% patients affected). There is a well-recognised association between the two diseases (3, 11, 17, 25, 26).

One suggestion for the correlation between the 2 disorders is the coexistence of HLA molecules in both diseases (25). HLA DR3 (25, 26), HLA B8 (25) and HLA DQ8 (26) have been implicated. Another possibility is that the autoimmune reaction occurring in the presence of gluten in coeliac patients promotes the development of autoimmune disorders (27). Furthermore it was shown that these autoantibodies disappear on withdrawal of gluten from the diet (28). Many of the coeliac-associated disorders are autoimmune in nature and 34% of patients in the study were found to have a coexisting autoimmune disorder. This concurs with a study by Collin et al. (29), where 28% cases had a disease considered to be of autoimmune origin.

Arthritis and affective disorders were jointly the second most common diseases found among the cases studied.

Although, rheumatoid arthritis is frequently quoted as being coeliac-associated (18, 30, 31). A literature review showed little evidence to support this association (32, 33). However, there may be evidence to support the concept of an enteropathic arthritis as described by Lubrano et al. (31).

Nineteen percent of cases in this study had been diagnosed with an affective disorder. However, Fera et al. (34) suggest that affective disorders in coeliac disease are associated with initial diagnosis and adjustment to the gluten-free diet and thus recommend preventative psychiatric interventions.

The association between coeliac disease and IgA deficiency is widely accepted (29, 35, 36) and this immunological disorder was common among the group. The reason for this connection is unclear and it is not certain whether this is due to a common genetic factor or whether one condition predisposes to the other. The HLA alleles B8, DR3, DR7 and DQ2 are thought to be likely candidates for a genetic cause as they are prevalent in both conditions (29, 35). The primary concern with this association is the capacity for missing cases of coeliac disease as serology becomes the principal form of screening. Thus Gillett et al. (36) argue that biopsy confirmation of diagnosis remains essential.

Although the associations between type 1 diabetes mellitus and Sjögren's syndrome with coeliac disease are well documented (3, 8, 11, 22, 25), neither of these diseases were found among cases in this study. This is most likely attributable to small sample size.

Pernicious anaemia and primary biliary cirrhosis are among the less frequently quoted coeliac-associated disorders and present in only 3 and 2 patients studied here respectively. Elevated transaminase is frequently found at diagnosis while liver damage, characterised by inflammation and steatosis, has been shown to resolve on a gluten-free diet (37, 38).

The association between pernicious anaemia and coeliac disease is somewhat underreported (39). Three cases of pernicious anaemia were found in this study.

The relationship between inflammatory bowel disease and coeliac disease is well recognised (40). Inflammatory bowel disease is more prevalent in first degree relatives of coeliac patients than the normal population (41). Although, only one of the 32 patients studied here had proven ulcerative colitis, none of the patients had Crohns disease.

There is a possible association between coeliac disease and sarcoidosis (25, 42). One patient in this study had sarcoidosis which, given the rarity of this disease, may support these previous hypotheses.

Biopsy was 97% specific, and probably equivocal in only one case (increase in intraepithelial lymphocyte). In this isolated case anti-tTG was significantly raised at 120.3 U/ml (reference range 0-10). The patient had classical symptoms of abdominal discomfort and diarrhoea noted to occur following ingestion of wheat. This patients serology was normalised and symptoms had disappeared on the gluten free diet.

Of the positive biopsies, most patients did not have total villous atrophy, the majority having partial villous atrophy. An association between histological grade and anti-gliadin antibody levels at diagnosis was found to be statistically significant. This would add support to the argument of those who believe serology tests could be used to screen for coeliac disease (43).

This study showed the sensitivity of EMA to be 68% and that of AGA to be 75%. In combination these two antibodies gave 91% sensitivity (95% CI 79.3-102.7%). The

sensitivity of tissue anti-tTG was 90% (95% CI 71.4-108.5%). This demonstrates the tests to be 100% sensitive in combination, be it with a small sample size.

Previous studies show EMA to be 68-100% specific (44), and, when used in conjunction with AGA, a 98% sensitivity is quoted (8). Thus the results obtained here can be seen not to significantly differ from those obtained from previous studies (45).

Serology may be negative in cases of IgA deficiency and hypogammaglobulinaemia (46). Although there were no IgA-deficient patients in the study, one patient had hypogammaglobulinaemia. This patient however was not tested for anti-tTG at the time of diagnosis but did have positive EMA and AGA.

The findings of this audit suggest that patients with non-specific symptoms such as fatigue and generalised abdominal pain presenting to their general practitioner should undergo serological testing for coeliac disease.

By more widespread awareness of the varied spectrum of presentations of patients with coeliac disease among general practitioners, more patients with coeliac disease could be diagnosed earlier. Hence risks of developing complications could be markedly reduced with a gluten-free diet.

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Figure 1: Distribution of age at diagnosis

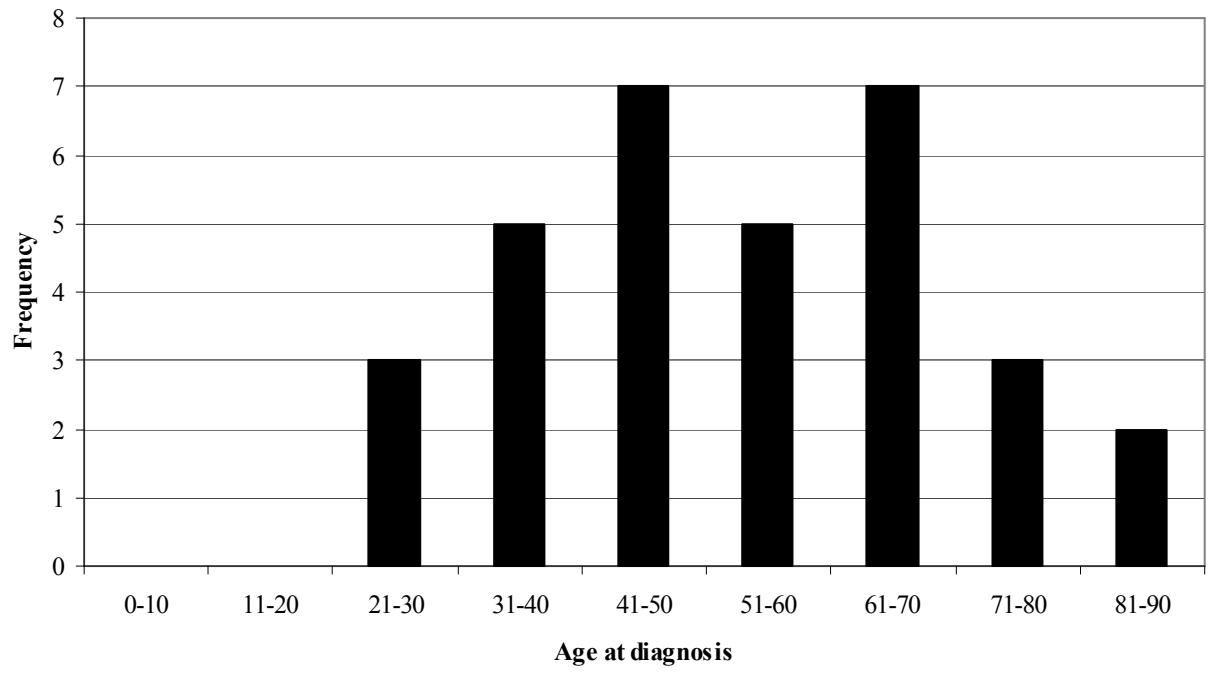


Figure 2: Source of referral

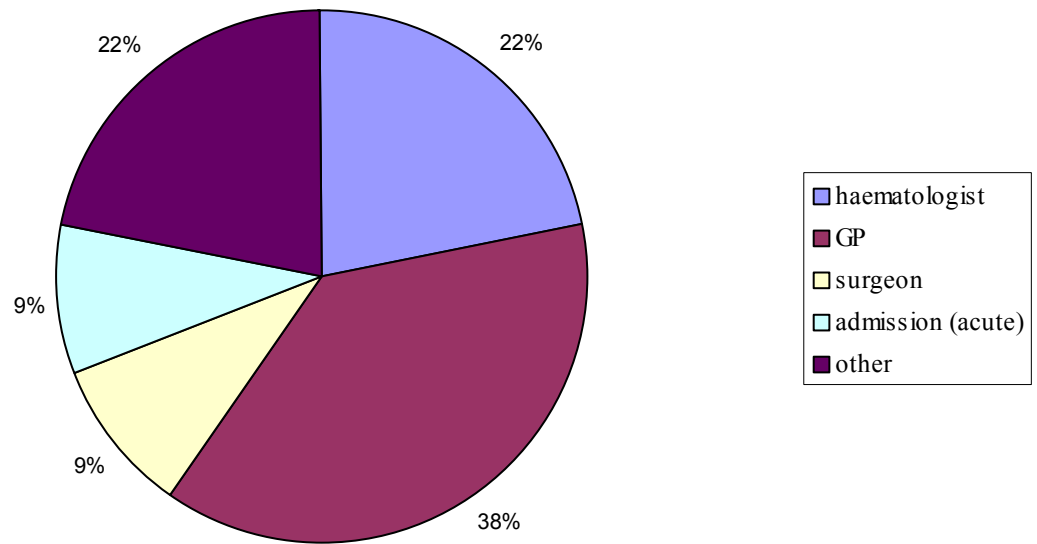


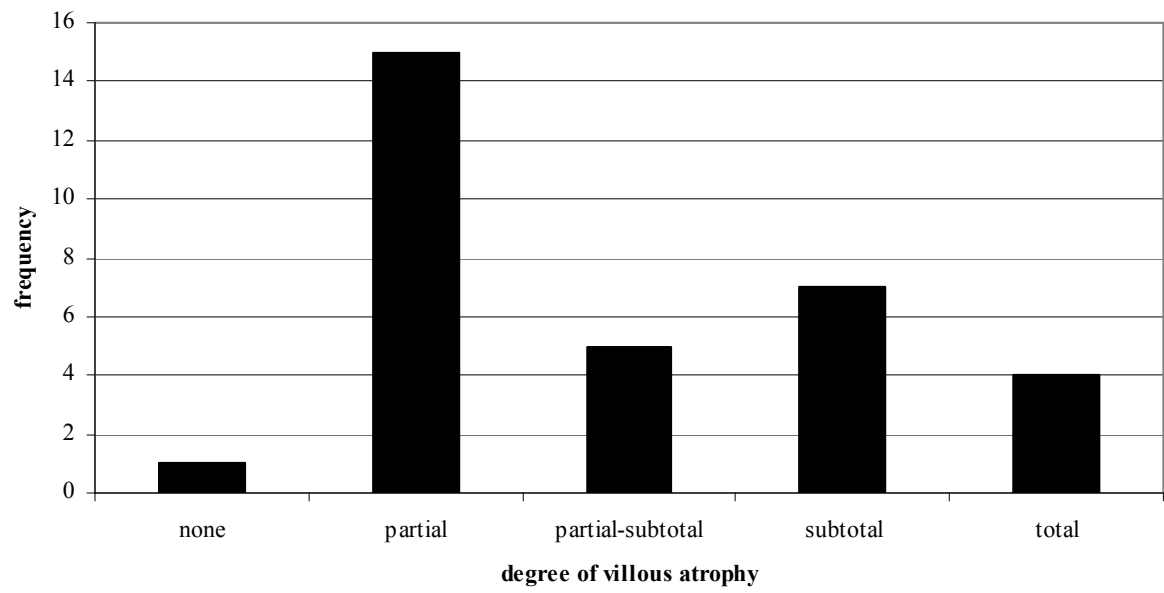
Figure 3: Findings at biopsy

Table - Comparison between the presenting complaints of patients in this study compared to those in the study of Zipser et al.

Complaint	Current study (%)	<i>Zipser et al (%)</i>
Anaemia	66	63
Abdominal pain or discomfort	41	77
Diarrhoea	38	52
Fatigue	31	82
Nausea and/or vomiting	28	46
Weight loss	28	55
Depression	19	46
Generalised aches and pains	19	42