Coeliac disease in primary care: case finding study

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Abstract

Objectives To provide evidence of underdiagnosis of coeliac disease and to describe the main presenting symptoms of coeliac disease in primary care.

Design Case finding in a primary care setting by testing for coeliac disease by using the endomysial antibody test.

Setting Nine surgeries in and around a market town in central England, serving a population of 70 000.

Participants First 1000 patients screened from October 1996 to October 1997.

Outcome measures Determination of endomysial antibody titre of patients fulfilling the study criteria, followed by small intestine biopsy of those with positive results.

Results The 30 patients (out of 1000 samples) with positive results on the endomysial antibody test all had histological confirmation on small intestine biopsy. The commonest mode of presentation (15/30) was anaemia of varying severity. Most patients (25/30) presented with non-gastrointestinal symptoms. Specificity of the endomysial antibody test was 30/30.

Conclusions Underdiagnosis and misdiagnosis of coeliac disease are common in general practice and often result in protracted and unnecessary morbidity. Serological screening in primary care will uncover a large proportion of patients with this condition and should be made widely available and publicised. Coeliac disease should be considered in patients who have anaemia or are tired all the time, especially when there is a family history of the disease.

Introduction

Most gastroenterologists recognise that Samuel Gee's description of coeliac disease in 1888¹ is now an uncommon presentation—but most general practitioners' image of coeliac disease is still of this classic form. Recent advances, driven by serological assays,² have led to the realisation that clinically overt cases represent only a small proportion of patients with the disorder. In addition to the classic and the atypical forms of coeliac disease, silent and latent forms have been described.³ Underdiagnosis in the community is due to lack of awareness of the heterogeneity of presentation as well as underuse of serological tests, particularly by general practitioners.^{4 5}

We used endomysial antibody tests in patients attending primary care to detect coeliac disease. From

the cases we found, we describe characteristics of patients with possible coeliac disease.

Method

Participants

The study was carried out in the market town of Banbury and the surrounding villages of Cropredy, Bloxham, and Sibford Gower and the town of Brackley. The nine participating surgeries served a population of 70 000. The population characteristics are typical of central England, with a low immigration rate.

From October 1996 to October 1997, 1000 blood samples were sent for serological screening from patients fulfilling the entry criteria for the study. The criteria were irritable bowel syndrome; anaemia (haemoglobin <115 g/l in female patients and <120 g/l in male patients; family history of coeliac disease; malabsorption symptoms or diarrhoea; fatigue or "tired all the time"; thyroid disease or diabetes; weight loss, short stature, or failure to thrive; epilepsy, infertility, arthralgia, or eczema. This list of criteria was derived from a literature search (done through Medline) and takes into consideration the different modes of presentation possible in a general practice setting.

Ethical approval was obtained from the Oxford medical ethics committee. The potential importance of a positive result was explained to all participants by their general practitioners, and patients' verbal consent was obtained.

Laboratory testing

Endomysial antibodies (EMA) were detected with indirect immunofluorescence. Cryostat sections of distal primate oesophagus were used as substrate, and serum diluted 1:5 in phosphate buffered saline was tested. Slides were washed with phosphate buffered saline and then incubated with goat anti-human IgA (Incstar, Wokingham) at predetermined dilution. Positive samples were identified by the characteristic reticulin-like staining pattern surrounding the oesophageal submucosal smooth muscle bundles. Serum titre of IgA (Beckman, Wycombe) was determined to identify cases of IgA deficiency.

Patients with positive results on the endomysial antibody test were referred for biopsy for confirmation. In those with low titres of IgA (<0.3 mg/l), IgG antigliadin antibody was estimated, as endomysial antibody results were considered unreliable in cases of IgA deficiency.

Small intestine biopsy

Biopsy specimens were taken with a Crosby capsule in the conventional way, either without sedation and steered under fluoroscopic control or by introducing the capsule via an endoscope under sedation. In two cases, distal duodenal specimens were taken at upper gastrointestinal endoscopy. All specimens were reviewed by a consultant histopathologist (NM).

Results

The mean age was 49.9 years for the 271 male patients (range 1-84 years) and 45.2 years (range 6 months to 85 years) for the 729 female patients. Of all patients screened, 5.3% were <10 years old and 3.1% were aged 80-90. The male:female ratio was 1:2.7.

A total of 30 patients (8 male patients and 22 female patients) had positive results on endomysial antibody tests. All consented to small intestine biopsies, and in all 30 patients these showed histological features consistent with a diagnosis of coeliac disease. (In comparison, seven cases of coeliac disease had been diagnosed at the local district general hospital in the preceeding 12 month; the resulting fourfold increase in incidence was solely due to active case finding during the study year.)

Table 1 shows the characteristics of the patients with positive results on the endomysial antibody tests and the reason for testing, divided into primary and

secondary reasons for screening. Case 4 was unwell for 9 months and saw six specialists privately before the diagnosis was made. Case 14 similarly visited the general practitioner frequently over many years with sometimes bizarre neurological symptoms, a presentation now known to be associated with coeliac disease.⁶ Most patients (25/30) did not present with intestinal symptoms, and general practitioners would not have suspected coeliac disease. The severity of symptoms did not always correlate with the severity of histological findings (cases 1, 3, and 6). Case 25 had minimal histological changes of increased intraepithelial lymphocytes (confirmed by two histopathologists). She was screened on the basis of a family history of coeliac disease (brother) and bowel cancer (six first degree relatives affected in the last two generations). She was positive for HLA DQB1*0201 and DQA*0501, alleles known to be primarily associated with coeliac disease.⁷ She fulfils the criteria for the label of potential coeliac—that is, people with positive serology results plus a positive family history with a high intraepithelial lymphocyte count on small intestine biopsy.³

Table 2 shows the breakdown of the major case finding categories. Of the 126 patients tested who had anaemia of varying degrees (usually with microcytosis), 15 patients had a primary presentation and three had a secondary presentation of anaemia, and three others (cases 8, 13, 30) had an incidental finding of anaemia.

Table 1 Characteristics of patients with positive results on endomysial antibody testing

Case No	Sex	Age (years)	Presentation		Haemoglobin concentration (g/l)	Mean cell volume	Histology
			Primary	Secondary			
1	F	46	Anaemia		110	78.0	Subtotal villous atrophy
2	M	42	Diarrhoea		142	91.6	Subtotal villous atrophy
3	F	19	"Tired all the time"	Mild anaemia	110	78.8	Total villous atrophy
4	M	60	"Tired all the time" (chronic fatigue syndrome)	Weight loss	147	98.2	Total villous atrophy
5	F	42	Anaemia (intermittent)	Family history	142	79.8	Subtotal villous atrophy
6	F	38	"Tired all the time"		116	89.1	Total villous atrophy
7	F	36	Anaemia	"Tired all the time"	104	78.2	Subtotal villous atrophy
8	F	73	"Tired all the time"	Hypothyroidism	107	104.0	Subtotal villous atrophy
9	F	37	Malabsorption	Anaemia	81	63.0	Total villous atrophy
10	F	47	Anaemia	"Tired all the time"	80	78.6	Total villous atrophy
11	F	34	Anaemia		70	70.2	Subtotal villous atrophy
12	F	21	Thyroid problem	Past anaemia	123	88.7	Total villous atrophy
13	F	72	Malabsorption		96	86.0	Subtotal villous atrophy
14	M	51	Anaemia (past)	Odd neurology	118	74.7	Total villous atrophy
15	F	37	Anaemia (pregnancy)		98	79.7	Subtotal villous atrophy
16	M	18	Family history (mother)	"Tired all the time"	138	91.7	Partial villous atrophy
17	F	54	Anaemia	Family history (sister)	91	71.4	Subtotal villous atrophy
18	F	44	Anaemia		83	69.3	Total villous atrophy
19	F	28	Anaemia		74	69.4	Subtotal villous atrophy
20	F	45	"Tired all the time" (chronic fatigue syndrome)		NA	NA	Subtotal villous atrophy
21	F	1	Malabsorption	Failure to thrive	132	87.2	Total villous atrophy
22	M	58	Anaemia (past)	Weight loss	152	89.3	Subtotal villous atrophy
23	F	54	Anaemia	Family history	96	63.7	Subtotal villous atrophy
24	F	44	Anaemia		88	64.7	Mild villous atrophy
25	F	59	Family history (brother)		133	87.2	Increased intraepithelial lymphocytes
26	F	50	Unexplained macrocytosis		125	97.9	Total villous atrophy
27	F	32	Anaemia		91	67.1	Total villous atrophy
28	M	64	Anaemia (mild)		117	89.6	Subtotal villous atrophy
29	M	52	Malabsorption		119	83.8	Total villous atrophy
30	M	27	"Tired all the time"	Family history Liver function test results raised	108	83.4	Total villous atrophy

NA=not available.

Table 2 Major case finding categories. Values are numbers of patients with the disease and numbers of patients screened (percentages; 95% confidence intervals)

Category	Male patients	Female patients	Total
Irritable bowel syndrome	0/42	0/90	0/132*
Anaemia	3/13 (23)	12/113 (11)	15/126 (12; 6 to 18)
Family history of coeliac disease	1/12 (9)	1/16 (6)	2/28 (7; 0 to 17)
Malabsorption or diarrhoea	2/39 (5)	3/54 (6)	5/93 (5; 1 to 10)
Fatigue ("tired all the time")	2/63 (3)	4/266 (2)	6/329 (1.8; 0.4 to 3.3)
Thyroid or diabetes	0/65	1/92 (1)	1/157 (0.6; 0 to 2)
Weight loss, short stature, failure to thrive†	0/11	0/25	0/36
Other (epilepsy, infertility, abnormal blood test, arthralgia)	0/26	0/73	1/99
Total	8/271 (3)	22/729 (3)	30/1000 (3.0; 1.9 to 4.1)

*Prior diagnoses. †Paediatric.

Thus 21 out of 30 patients had a history of anaemia (see table 1).

The second commonest presentation was the patient who is "tired all the time." Of the 329 patients tested, six patients found to have coeliac disease presented primarily with this symptom, and in three this was a secondary symptom (see table 1).

Of the 28 patients tested because of a family history of coeliac disease, six patients (two in whom the family history was a primary reason for screening and four in whom it was secondary) had positive results on endomysial antibody tests.

All 30 patients with positive results on endomysial antibody tests had positive biopsy results, giving a specificity of 100%. Sensitivity cannot be calculated in this study since patients with negative results on endomysial antibody tests did not undergo biopsy. Sensitivity in previous adult studies ranges from 89% to 100% and specificity of the endomysial antibody test ranges from 94% to 100%.⁸ Until sensitivity and specificity of the endomysial antibody test are firmly established in our locality, jejunal biopsy remains the test for diagnosis.

Four patients, all women, were identified as IgA deficient, and further investigations of these patients is proceeding.

Discussion

This study represents the first case finding study for coeliac disease in a community in the United Kingdom. Testing for endomysial antibody (with measurement of serum IgA) was chosen for the study because it is widely regarded as the best antibody test for coeliac disease.^{9 10}

Presenting symptoms

Although the study was of case finding rather than whole population screening, not all patients had symptoms—for example, patients with a family history and some with anaemia who reported vague ill health only on direct questioning. Presenting symptoms were more non-specific than in other published series on coeliac disease.^{11 12} In our study, of the 225 patients (22.5%) presenting with gastrointestinal symptoms, only five had coeliac disease, all in the malabsorption/diarrhoea category (93 samples). Surprisingly, none of the patients with irritable bowel symptoms (132 samples) had positive results, suggesting that coeliac disease rarely masquerades as the irritable bowel syndrome in general practice, although such a presentation is not unknown.

Our most important finding is the presence of anaemia: of patients who had this presentation, 11% of the female patients tested and 23% of male patients tested had coeliac disease. We recommend that endomysial antibody should be one of the first line investigations for unexplained anaemia in the community.

General practitioners will notice that "tired all the time" is among the main presenting symptoms. In a prospective study of 220 patients presenting to general practitioners with fatigue, three quarters had a history of emotional distress (depression or anxiety).¹³ However, abnormal results on laboratory tests were found in 19 patients, of whom eight had anaemia, three hypothyroidism, three infections, one glandular fever, and one carcinomatosis. Although psychosocial factors are by far the commonest cause of fatigue, general practitioners ought to be alert to the possibility of coeliac disease, particularly when there is anaemia. Cases 4 and 20 illustrate this potential pitfall—they were labelled as having chronic fatigue syndrome after long periods of feeling tired.

The average age of the adult patients with coeliac disease (excluding one girl aged 1 year) was 44 years; 43% were aged over 45 and 10% were over 60. Diagnostic delay in the older age group has been commented on by Hankey, who made the specific point that almost half of their patients had attended their general practitioners or hospital outpatient clinics for an average of 28 years with unexplained symptoms or blood test abnormalities.¹²

Table 3 Case finding for coeliac disease in general practice of 6000 adults

Target diagnostic group	Prevalence (%)	Target No for screening	Estimate of No actually screened	Screen efficiency (% of target No)	Study % new coeliac diagnoses in screened patients	Previous diagnoses + likely No of new cases
Irritable bowel syndrome	12 ¹⁴	720	55	7.6	0/132 (apply 0.5/133)	2 + 2.7
"Tired all the time" (fatigue)	7.5 ^{15 16}	450	137	30.5	6/329	0 + 8.2
Anaemia diagnosed 1996-7 (study period)	3.3*	56	5†	8.9	15/126	0 + 6.7
Anaemia diagnosed before Oct 1996	?	118‡	36†	30.5‡	15/126	1 + 14
Total		1344	233	17.3		3 + 31.6

The example of irritable bowel syndrome shows how to use this table. The literature gives a prevalence of 11-14%¹⁴; we have taken 12% for our calculation. The target number for screening in a practice with 6000 adult patients is therefore 720. Using the contribution of this practice to the study population (41.7% of participants), the number estimated to have been screened is 55 (41.7% of 132), giving a screening efficiency of 7.6% (55/720). The percentage of patients screened in the study who were diagnosed as having coeliac disease was applied to the target number (as no patient was diagnosed as having coeliac disease, an adjusted prevalence of 0.5/133 was applied to 720); this yields a likely 2.7 new cases of coeliac disease in target patients with the irritable bowel syndrome, which is added to the pre-existing 2 cases.

*197 diagnoses of anaemia after full blood counts; 56 of these not explained by case notes. †Actually screened. ‡Estimated.

Case finding

The clinical importance of the data gathered is best illustrated by analysing in detail the subgroup of patients tested in one of the participating practices, where awareness of coeliac disease is relatively high. The practice, which contributed 417 samples (41.7%) to the study, has 8000 patients, of whom 6000 are adults (age > 16 years), with a male:female ratio of 1:1. Before the study there were eight known cases of coeliac disease (six adults and two children). Two of the adults presented with irritable bowel syndrome; one presented with anaemia, two with malabsorption, and one with dermatitis herpetiformis.

Table 3 shows the case finding for coeliac disease that might be expected in a general practice of 6000 adult patients if screening was targeted on the specific diagnostic groups of irritable bowel syndrome, tired all the time, and anaemia. Most cases of coeliac disease in our study included anaemia, so we have analysed the data in greater detail. In the study year, of the 971 samples sent to the Horton hospital by the practice for full blood counts, 197 patients were anaemic by our definition. Review of their clinical details showed a range of conditions from rheumatoid arthritis, bleeding tendencies, cancer, and recent surgery, with 56 cases unexplained. Therefore, the incidence of new cases of anaemia during the study period was 3.3% (197/6000), with 0.9% (56/6000) unexplained. Of the 56 eligible for screening, only five entered the study, giving a screening efficiency of 8.9%. However, we also need to consider past anaemia as an entry criterion. An estimated target for screening based on the 30.5% achieved for "tired all the time" would represent 118 estimated target cases (36 (patients known to have had anaemia who were screened) $\times$ 100/30.5). With 100% screening efficiency, we predict that in a practice with 6000 adult patients, present and past anaemia would generate a further 20.7 cases of coeliac disease.

Overall, 100% screening efficiency would have identified a further 31.6 cases of coeliac disease in patients with anaemia, who were tired all the time, or had irritable bowel syndrome. As the prevalence of malabsorption and positive family history are not calculable with any degree of accuracy, we have not attempted to apply the statistical analysis to these presentations.

The tip of the iceberg?

Prevalence in other countries varies widely, with the highest in Italy and the west of Ireland, both quoted as 1:300.^{17 18} As more patients are screened in Britain, the ultimate prevalence may be similar.

The cost implications of increased numbers of patients diagnosed as having coeliac disease, measured in terms of increased workload for gastroenterologists and dietitians, as well as the prescribing costs of gluten free products, need to be balanced against the cost of delayed diagnosis and complications such as osteoporosis, infertility, and malignancy.¹⁹ An endomysial antibody test costs around £10 and the cost of biopsy is estimated as £150. We feel that these expenses are justified, given that coeliac disease is not only a treatable disease but also has serious preventable long term complications.

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Key messages

- General practitioners currently see many people with undiagnosed coeliac disease
- The most likely presentation is a combination of microcytic anaemia, past or present, a family history of the disease, and feeling tired all the time
- Estimations of endomysial antibody and IgA are reliable diagnostic tools
- The prevalence of coeliac disease in Britain is higher than the accepted figure of 1:1000 population
- Increased awareness of the extra intestinal manifestations of coeliac disease, coupled with a low threshold for serological testing, will uncover a large portion of undiagnosed coeliac disease

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Contributors: HH designed the study, coordinated the primary care aspect, and wrote the paper. GB helped to design the study, coordinated the EMA assays, collected and interpreted data, wrote the paper, and is guarantor. PF coordinated the secondary care aspect of the study and did most of the biopsies and helped analyse data. NM coordinated histological aspects, interpreted biopsies, and analysed data. DJ helped design the study, performed some biopsies, interpreted data, and helped finalise the draft.

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