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Coeliac disease detected by screening is not silent—simply unrecognized

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Summary

Coeliac disease (CD) is associated with a wide spectrum of clinical presentation and may be overlooked as a diagnosis. There is some evidence that untreated CD is associated with a doubling of mortality, largely due to an increase in the incidence of malignancy and small intestinal lymphoma, which is decreased by a strict gluten-free diet. We studied the clinical features of screening-detected coeliacs compared to age- and sex-matched controls as a 3-year follow-up to a population screening survey, and followed-up subjects who had had CD-associated serology 11 years previously to determine whether they have CD or an increased mortality rate compared to the general population. Samples of the general population (MONICA 1991 and 1983) were screened for CD-associated serology and followed-up after 3 and 11 years, respectively, and assessed by a clinical questionnaire, screening blood tests and jejunal biopsy. Mortality rates for 'all deaths' and 'cancer deaths' were compared in subjects with positive serology in 1983 with reference to the general population. Thirteen coeliacs were diagnosed by villous atrophy following screening, compared to two patients with clinically detected CD, giving a prevalence of 1 : 122. Clinical features or laboratory parameters were not indicative of CD compared to controls. Subjects with positive serology followed up after 11 years did not have an excess mortality for either cancer deaths or all causes of death. Screening-detected CD is rarely silent and may be associated with significant symptoms and morbidity. In this limited study with small numbers, there does not appear to be an increased mortality from screening-detected CD, although the follow-up may be too short to detect any difference.

Introduction

It is well recognized that coeliac disease may present a diagnostic challenge to clinicians. This is because the spectrum of clinical presentation is broad and while some patients have evidence of severe malabsorption, others have minimal symptoms, or are completely asymptomatic.[1] Since the clinical presentation may be subtle and there are no diagnostic symptoms or signs, many cases may remain undiagnosed.[1] Coeliac disease may be complicated by malignancy, and there is a strong suggestion that this increased risk is reduced by strict dietary adherence to a gluten-free diet for 5 years.[2] This should lead to a determined search for patients with undiagnosed coeliac disease who could benefit from a gluten-free diet.

IgA antibodies to gliadin (AGA), endomysium (EMA) and reticulin (ARA) have been used alone and in various combinations to screen for this condition. We have previously reported on the value of AGA and EMA in hospital outpatients suspected of having coeliac disease.[3] In a separate study, we have used ARA and AGA to identify previously undiagnosed patients with gluten-sensitive enteropathy who did not have gastrointestinal symptoms but with significant morbidity.[4]

In an attempt to estimate more accurately the prevalence of subclinical coeliac disease in our community, we have reported on the results of screening a large-scale population survey (Belfast MONICA Project 1991 survey) with IgA-AGA, IgA-EMA and IgA-ARA.[5] IgA-AGA was present in 5.7%

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of the adult population, compared with IgA-EMA (1.2%) and IgA-ARA (0.4%). Subsequently we found that the prevalence of coeliac disease was at least 1 : 122 in the sample population.[6]

In this study we report on the clinical features of these screening-detected coeliacs, to determine whether symptom profile and laboratory parameters were indicative of coeliac disease. In addition, we followed-up subjects with positive serology detected by population screening 11 years previously to determine the prevalence of coeliac disease in this group, and to assess if there was an excess mortality rate in this group compared to the general population.

Methods

In Northern Ireland, the Belfast MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Project was set up as part of a multi-centred, international study to determine risk factors for coronary heart disease in the adult population. This population was selected at random by means of a computer programme from patients contained on the Northern Ireland Central Service Agency's General Practitioners' list. The latest survey, MONICA III, began in October 1991 and included 2004 subjects in the age range 25–64 years, 1823 of whom had serum samples available to us for analysis. The first survey, MONICA I, began in October 1983 and included 1204 subjects.

Serum samples were taken as part of the initial screening of subjects in the MONICA surveys for serum cholesterol. These samples were centrifuged, aliquoted and stored at $-70\,^{\circ}C$ until tested. Serological testing was carried out during the period January 1994 to June 1994 for samples from both 1991 and 1983 surveys as previously described.[3]

Determination of IgA antibodies to gliadin (IgA-AGA) was carried out by enzyme-linked immunosorbent assay (ELISA; Labmaster). Results were expressed in ELISA units (EU) with a normal range of 0–99 (97.5th centile).

Using indirect immunofluorescence, sera were initially screened at a dilution of 1 : 20 for the presence of antireticulin antibody of the R1 type (ARA) in the IgA class using composite sections of rat liver, kidney and mouse stomach (BioDiagnostics) and fluorescein-conjugated antihuman globulin (Dako). Positive sera were titrated further.

EMA in the IgA class was detected by indirect immunofluorescence using monkey oesophagus (BioDiagnostics) as antigen. Sera were initially tested at a dilution of 1 : 2 and any positives tested at dilutions 1 : 5, 1 : 10, 1 : 20 and 1 : 40. Positivity was taken as a titre of 1 : 5 or greater.

At the follow-up interview, subjects were asked to fill in a structured clinical questionnaire designed to assess symptoms and signs of malabsorption such as diarrhoea, weight loss, anaemia, extreme lethargy and other gastrointestinal symptoms. A record was made of previous medical problems and current medications. Neither the study subjects nor the physician were aware of the results of the serological screening at the time of the initial interview. A blood sample was obtained for full blood picture, urea and electrolytes, liver function tests; bone profile; iron status; serum B12; serum and red-cell folate. General Practice notes were reviewed to ascertain the presence or absence of attendances with diarrhoea, fatigue, anaemia or weight loss, the number of visits (regardless of the reason) within a fixed 2-year period (1 November 1992–30 October 1994) and the presence or absence of any relevant laboratory investigations.

All subjects were invited to attend for a small-intestinal biopsy which was carried out using a Watson–Crosby capsule placed endoscopically in the proximal jejunum using an Olympus videoendoscope. Each specimen was labelled with the subject's biopsy number only and the pathologist was blind to all patient details and their serology results. Enteropathy consistent with coeliac disease was considered to include severe partial villous atrophy, sub-total or total villous atrophy.

Symptom frequencies and responses with two possible categorical variables were compared using McNemar's test for case-control pairs. Continuous variables were compared between case-control pairs using paired t-test (parametric) or Wilcoxon matched pairs test (non-parametric) as appropriate. A value of $p < 0.05$ was considered significant.

This study was approved by the Research Ethics Committee of the Queen's University of Belfast.

MONICA 1991 survey follow-up: patients

One hundred and thirteen (6.2%) of the 1823 subjects tested in the MONICA 1991 survey had at least one positive coeliac-disease-associated antibody detectable at significant titre: 84 subjects were positive for IgA-AGA, seven for IgA-EMA, six for IgA-ARA, nine had both IgA-AGA and IgA-EMA, one had both IgA-AGA and IgA-ARA, four had IgA-ARA and IgA-EMA, and two subjects had all three antibodies. These subjects were identified as the study population. Subjects were followed-up approximately 3 years (mean 3.4 years, range 2.4–3.9) after the initial screening programme. Of the 113 subjects identified, General Practitioners were unwilling for eight subjects to be included, 15 subjects declined to participate, and one subject had moved to England. In addition, 113 age- and sex-matched subjects with

negative coeliac-disease-associated antibody serology were selected at random from the same survey to act as control subjects. Of these, General Practitioners were unwilling for four subjects to be included, 19 subjects declined to participate and one subject had died. Therefore 89 controls were available for follow-up.

The 1991 follow-up study population therefore comprises 89 subjects (45 male, mean age 50.9 years) with positive serology who were paired with 89 age- and sex-matched controls (45 male, mean age 51.1 years).

MONICA 1983 survey follow-up: patients

Of the 102 subjects (52 male, mean age 60.1 years) with positive serology in the initial 1983 MONICA screening programme, 72 subjects (34 male, mean age 58.1 years) consented to clinical follow-up. The follow-up study was carried out 11.6 years (range 11.3–11.9 years) following the initial screening programme. Of the remaining 30 subjects, General Practitioners were unwilling for seven (AGA positive) to be followed-up, 10 subjects did not give consent to clinical follow-up and 13 had died in the interim period. No controls were included in the 1983 survey follow-up.

Results

MONICA 1991 follow-up study

Two subjects had a diagnosis of coeliac disease made prior to follow-up of the screening programme in 1994. A 60-year old man (AGA + EMA positive at screening) presented with anaemia (Hb 10.5 g/dl) due to iron and folate deficiency. Dietary gluten exclusion led to a rise in haemoglobin (10.5 to 11.9 g/dl) and a partial recovery of the small intestinal mucosa on a subsequent biopsy. The second subject, a 65-year-old lady (EMA + ARA on screening) with insulin-dependent diabetes mellitus and hypothyroidism, presented with iron-deficiency anaemia (Hb 8.7 g/dl) which subsequently rose to 13.3 g/dl on a gluten-free diet. These two subjects are excluded from further analysis.

Of 87 subjects who consented to clinical follow-up and were not known to be coeliac, 51 (26 male, mean age 50.2 years) gave consent for jejunal biopsy. Thirteen of these (four male, mean age 53.2 years) had enteropathy consistent with coeliac disease. There were no significant differences between the symptom frequencies reported by the untreated coeliac group and age- and sex-matched controls. Two coeliac patients had a past history of neoplasia (cervical carcinoma-in-situ, basal cell carcinoma) and one other had a history of a fractured lumbar vertebra secondary to trauma.

Although mean haemoglobin (13.0 vs. 13.9, $p = 0.02$) was significantly lower in the untreated coeliac group compared to controls, it was still within the established normal range in our laboratory. None of the other laboratory parameters were significantly different between the two groups although serum folate levels (5.3 vs. 7.1, $p = 0.09$) and serum ferritin levels (28.7 vs. 92.5, $p = 0.1$) tended to be lower in the untreated coeliac group.

Of the 13 coeliac patients, four (CD 5,6,8,9) (Table 1) were relatively asymptomatic, apart from flatulence in two. However one of these four asymptomatic patients had evidence of folate deficiency (CD 5) as detected by red-cell folate levels (< 110 mg/l) and two (CD 6,9) had evidence of iron deficiency (ferritin < 10 mg/l) (Table 2). One of the coeliacs (CD 6) with iron deficiency was anaemic on screening (Hb 8.4 g/dl), her only symptom being shortness of breath which the patient had attributed to smoking. Of the remaining nine patients with symptoms, two subjects (CD 2,3) had folate deficiency and one had iron deficiency with haemoglobin concentration 11.9 g/dl (CD 1).

Four of the thirteen coeliacs had previously attended hospital with features consistent with coeliac disease. CD 1 (F, 61 years) had attended a teaching hospital over a 30-year period initially with diarrhoea and folate deficiency. Initial screening tests for malabsorption were negative and jejunal biopsy was considered, but not performed. Follow-up during this study revealed iron deficiency alone. CD 2 (M, 51 years) had recently been admitted to hospital with pneumonia, at which time he was noted to have a macrocytosis and folate deficiency. No further investigations were carried out. Folate deficiency was also found to be persistent during this follow-up study. CD 3 (F, 36 years) had attended a hospital out-patient department with diarrhoea and weight loss. Initial screening tests for malabsorption were normal with the exception of folate deficiency. No serological tests for coeliac disease or jejunal biopsy were performed. CD 7 (F, 59 years) had several acute admissions to hospital with abdominal pain, and this was attributed to diverticular disease despite minimal evidence on barium enema. No further investigations had been performed.

Two coeliac patients (CD 5, CD 10) had a family history of coeliac disease, with the mother affected in both cases. One of these was asymptomatic (CD 5). One of the other coeliacs (CD 6) had a history of insulin-dependent diabetes mellitus. These three coeliac patients would have been detected if screening 'at risk' groups had been performed.

Comparing the untreated coeliac group with controls, there were no significant differences between

Table 1 Symptom profiles of 13 screening-detected coeliac patients

CD	Age	Sex	BMI	Childhood ill-health	Failure to thrive	Previous anaemia	Weight loss	Diarrhoea	Lethargy	Flatulence	Mouth ulcers
1	61	F	21.8	Y	N	Y	N	Y	Y	Y	Y
2	51	M	18.4	Y	Y	N	Y	N	N	Y	N
3	36	F	18.9	Y	Y	Y	Y	Y	N	Y	N
4	58	F	21.6	N	N	Y	N	N	N	N	Y
5	45	M	26.3	N	N	N	N	N	N	Y	N
6	56	F	30.1	N	N	N	N	N	N	N	N
7	59	F	26.9	N	N	Y	N	Y	N	Y	Y
8	39	M	33.2	N	N	N	N	N	N	N	N
9	44	F	19.8	N	N	N	N	N	N	Y	N
10	61	F	24.8	Y	N	Y	N	N	N	Y	N
11	56	M	21.1	N	Y	N	N	N	Y	Y	N
12	59	F	18.6	N	N	Y	N	N	N	Y	N
13	67	F	21.0	N	N	Y	N	N	Y	Y	Y
Totals				4	3	7	2	3	3	10	4

BMI, body mass index; Y, present; N, absent.

Table 2 Nutritional deficiencies, previous hospital investigations and family histories of untreated coeliac patients

CD	Age	Sex	Present anaemia	Folate deficiency	Iron deficiency	Hospital investigation	Family history
1	61	F	Y	N	Y	Diarrhoea	
2	51	M	N	Y	N	Folate deficiency	
3	36	F	N	Y	N	?Malabsorption	
4	58	F	N	N	N	N	
5	45	M	N	Y	N	N	Mother
6	56	F	Y	N	Y	N	
7	59	F	N	N	N	Abdominal pain	
8	39	M	N	N	N	N	
9	44	F	Y	N	Y	N	
10	61	F	N	N	N	N	Mother
11	56	M	N	N	N	N	
12	59	F	N	N	N	N	
13	67	F	N	N	N	N	
Totals			3	3	3	4	2

Y, present; N, absent.

attendances at their General Practitioners for diarrhoea, fatigue, anaemia or weight loss. The number of attendances in a fixed 2-year period was similar for both groups (7.8 vs. 8.1, $p=0.94$). Thyroid function tests were recorded in eight of the coeliac group and two of the control group ($p=0.07$). Full blood picture was tested in a higher number of subjects in the control group compared with coeliacs, although this difference was not significant (12 vs. 7, $p=0.06$).

MONICA 1983 follow-up study

Of 72 subjects who consented to clinical follow-up and were not known to be coeliac, 20 gave consent for jejunal biopsy. Three of 20 subjects biopsied had villous atrophy on the initial biopsy. Of the three coeliacs, CD 14 (M, 37 years) has a positive family history (mother), a history of recent weight loss attributed to anxiety and evidence of folate deficiency (red-cell folate <110 mg/l). Initial serological profile was AGA + EMA (1 : 20) and this had persisted at 11-year follow-up, with the EMA titre rising to 1 : 40. CD 15 (F, 40 years) had symptoms of abdominal distension and evidence of iron deficiency (Ferritin <10 mg/l). Serological profile was AGA + EMA (1 : 10) + ARA (1 : 20) at initial screen, and this had persisted at 11-year follow-up with the EMA titre rising to 1 : 40. CD 16 (F, 61 years) was completely asymptomatic and had no nutritional deficiencies. Serological profile was EMA (1 : 40) + ARA (1 : 20) at initial screen and AGA + EMA (1 : 20) + ARA (1 : 40) at 11-year follow-up. After consideration, she was unwilling to commence a gluten-free diet. CD 14 and CD 15 have commenced a gluten-free diet with resulting weight gain in the first and a resolution of gastrointestinal symptoms in the second.

Notably one subject (LCD1; M, 50 years) with AGA + EMA (1 : 40) + ARA (1 : 80) at the time of the follow-up study had normal villous architecture following an out-patient assessment. He had a 20-year history of diarrhoea which was attributed to irritable bowel syndrome. On direct questioning, other symptoms included a history of 11 kg weight loss over an 18-month period, lethargy, mouth ulcers, abdominal distension and flatulence. Investigations revealed pancytopenia (Hb 5.7 g/dl, WCC 2.07×10^9/l, PLT 89×10^9/l) with iron deficiency (ferritin <10 μg/l), hypocalcaemia (Ca^{2+} 2.02 mmol/l) and raised alkaline phosphatase (ALP 253 U/l). AGA, EMA (1 : 40) and ARA (1 : 40) had persisted at follow-up. Despite the normal jejunal biopsy, he was commenced on a gluten-free diet with marked improvement in his symptoms. Subsequently he tolerated a limited gluten challenge (2 weeks), after which time his symptoms returned and the jejunal biopsy was repeated. This revealed sub-total villous atrophy and he was re-commenced on a gluten-free diet. He therefore had latent coeliac disease and subsequently developed overt enteropathy.

Mortality

There were 13 subjects (seven male; mean age at death 67.3 years, range 56–75) with positive serology who had died following the initial Belfast MONICA 1983 survey and prior to follow-up in 1995. Information relating to their cause of death was obtained from death certificates obtained from the General Register Office (DC 1–10) or General

Practitioner records (DC 11–12) if the death had not been registered (Table 3). In the case of DC 13, the death had not been registered with the General Register Office and no medical records were available for analysis.

Four patients (two male, mean age 67.5 years) died with a record of malignant disease on the death certificate. The malignant diseases were carcinoma of the pancreas (DC 2), carcinoma of stomach (DC 3), bile duct lymphoma (DC 4) and metastatic malignant melanoma (DC 6). In two cases (DC 1, DC 8) death certificates included evidence of fractures (pelvis, ribs), and in the latter case this is attributed specifically to chest trauma. As far as can be ascertained, none of the twelve deceased patients on whom information is available had a history of coeliac disease. On the basis of serological profile it seems possible that DC 13 (AGA + EMA + ARA) and possibly DC 1 (EMA + ARA) may have had a subclinical form of the disease, although this remains speculative.

To determine if this number of deaths was in excess of that expected, data were obtained from the Registrar General's Reports 1983–1994. Age-specific death rates per 1000 population for each year of the follow-up period were obtained for 'cancer deaths' and 'all deaths' by dividing the number of deaths in these two categories, in turn, by the mid-year population for each year 1983–1994. The contribution of each of the 102 subjects with positive serology to each of the different age bands was determined to assess 'person years at risk' and by multiplying this by the age-specific death rates per 1000 population, the total number of 'expected' deaths in the two categories in this sample population was obtained.

It was apparent that the number of 'cancer deaths' and 'all deaths' in the MONICA 1983 follow-up study was not in excess of that for the Northern Ireland population as a whole, based on data available from the Registrar General Reports. Four deaths were observed from cancer during the follow-up period, compared to the 4.28 (95% CI 1.09, 10.24) expected cancer deaths, giving a relative risk of cancer death of 0.94 (95% CI 0.3, 2.4). Thirteen deaths in total were observed during the follow-up period, compared to 14.11 (95% CI 6.92, 22.23) expected deaths, giving a relative risk of all deaths as 0.92 (95% CI 0.5, 1.6).

Discussion

Comparing the 13 untreated coeliacs detected by screening (1991 survey) with the age- and sex-

Table 3 Causes of death in MONICA subjects (1983 survey) who died between 1983 and 1995 with relation to serological markers for coeliac disease

DC	Age at death	Sex	Cause of death	Serology markers
1	61	F	Pulmonary emboli Deep venous thrombosis Pelvic fracture	EMA, ARA
2	68	M	Bronchopneumonia Carcinoma of pancreas	AGA 144
3	71	M	Carcinoma of stomach	AGA 115
4	66	F	Bile duct lymphoma	AGA 633
5	66	M	Myocardial infarction Coronary atherosclerosis	AGA 608
6	65	F	Metastatic disease Malignant melanoma	AGA 632
7	73	F	Ischaemic heart disease	AGA 131
8	56	F	Haemopericardium Multiple rib fractures Chest trauma	AGA 755
9	65	M	Ruptured aortic aneurysm Renal failure Bronchopneumonia	AGA 608
10	56	M	Coronary infarction Ischaemic heart disease Renal transplant	AGA 107
11	71	M	Cerebrovascular disease Alcoholic cirrhosis	AGA 127
12	75	M	Bronchopneumonia (Post-mortem)	AGA 632
13	69	F	No records	AGA 105, EMA, ARA

matched controls, there were no significant differences between symptom profile or laboratory parameters of these two groups, except for mean haemoglobin concentration which was significantly lower in the coeliacs. This underlines the fact that coeliac disease may be asymptomatic (4/13 patients) or associated with minimal symptoms in some cases. However, four of these 13 had attended hospital with features consistent with coeliac disease, but serological markers had not been tested and the diagnosis of coeliac disease had not been considered in any of the four patients. Therefore clinicians' awareness and knowledge of the wide clinical spectrum of the disease will determine how often the diagnosis is considered in patients who have features compatible with coeliac disease.

When the two patients are included who had a diagnosis of coeliac disease made prior to this follow-up study, the prevalence of adult coeliac disease in the MONICA 1991 study, follow-up is at least 15/1823 or 1/122. The ratio of coeliacs detected by screening to those diagnosed prior to follow-up of the screening programme is 13 : 2 or 6.5 : 1. This emphasizes that more coeliacs are currently unrecognized than recognized and is consistent with the iceberg analogy.[7]

All patients who had a jejunal biopsy performed with AGA + EMA (3 of 3), EMA + ARA (2 of 2) and AGA + EMA + ARA (2 of 2) detected by the 1991 screening programme had enteropathy. It is possible that all subjects with these three serological profiles who did not give consent for clinical or biopsy follow-up may have coeliac disease. Combining this prediction with the coeliacs diagnosed in the AGA group ($n = 4$) and EMA ($n = 2$) groups would yield a total of 21 patients or a prevalence of 1 in 87 (21/1823). Although this is perhaps an overestimate, it is clear from the biopsies which were performed that coeliac disease is much more prevalent than previous estimations for the United Kingdom, at least in Northern Ireland.

In total, four of 20 subjects biopsied from the 1983 survey follow-up had villous atrophy (sub-total villous atrophy in three, severe partial villous atrophy in one). The response rate of subjects (20 of 72) coming for jejunal biopsy in this group is disappointing. Two main factors probably accounted for this. Follow-up was about 11 years after the initial screening programme and since there did not appear to be any ill-effect on their health to date, subjects did not perceive a need to undergo an invasive test. In addition, the mean age of the 1983 survey follow-up subjects was 58.1 years (range 37–76 years) which was older than the 1991 subjects with positive serology (mean age 50.5 years, range 29–67 years). The 1983 survey subjects were enthusiastic about participating in a clinical questionnaire and blood tests, but were generally not so about invasive tests.

The relationship of serological profiles to enteropathy observed from the 1991 survey follow-up is not maintained in the 1983 survey follow-up. The 1983 survey follow-up led to the diagnosis of coeliac disease in only one of two subjects biopsied with AGA + EMA and EMA + ARA and both subjects with AGA + EMA + ARA. The estimated prevalence for coeliac disease from the 1983 survey is 4/1206 (1 : 301). If the two deceased subjects previously mentioned (DC 1 and DC 13) are included, the estimated prevalence rises to 1/201 (6/1206). This estimate is likely to be limited by the low uptake of jejunal biopsy in this group of subjects for the reasons discussed. However, it is clear from follow-up of the 1983 survey that antibody combinations such as EMA + ARA or AGA + EMA detected by population screening does not invariably indicate overt enteropathy, although follow-up of such subjects is required to detect latent coeliac disease.

The comparison of standardized mortality rates between the serology-positive subjects and the general population showed no significant difference. It raises the question as to whether subjects with screening-detected coeliac disease represent a specific subgroup of coeliac patients in whom the excess mortality of symptomatic coeliac disease is not observed.[8] However, we have only been able to study a small number of subjects, and the follow-up period of 11 years may be insufficient to detect a difference. A much larger study is required to clarify this point and to contribute to the issue of whether screening for coeliac disease should be recommended. At present it has been suggested that screening should be restricted to at-risk groups, for example, first-degree relatives of affected coeliacs[9] and insulin-dependent diabetics.[10]

As in other studies, it is clear that EMA is a better predictor of enteropathy than AGA or ARA. Although the sensitivity of EMA alone was 100% in the 1983 study, its sensitivity in the 1991 survey was only 69% (9/13 coeliacs). In the 1991 study, the combination of AGA with EMA improves the sensitivity to 100%, with a reduction in specificity (41%). The most comprehensive screening is therefore provided by testing for both EMA and AGA. However, it is evident that the use of even the best serological marker as a sole screening test will result in a small number of subjects with coeliac disease being missed as a result of false negative tests.

These studies highlight that coeliac disease is more prevalent than previous estimations. The question as to whether screening for coeliac disease should be encouraged in the general population is still unanswered. However, doctors need to have sufficient awareness of the possible presentations of

coeliac disease in order to diagnose as many cases as possible.

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