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RAPID COMMUNICATION

Gluten sensitive enteropathy in patients with iron deficiency anemia of unknown origin

Farhad Zamani, Mehdi Mohamadnejad, Ramin Shakeri, Afsaneh Amiri, Safa Najafi, Seyed Meysam Alimohamadi, Seyed Mohamad Tavangar, Ardeshir Ghavamzadeh, Reza Malekzadeh

Farhad Zamani, Mehdi Mohamadnejad, Afsaneh Amiri, Gastrointestinal and Liver Disease Research Centre, Iran University of Medical Sciences, Tehran, Iran
Ramin Shakeri, Seyed Meysam Alimohamadi, Reza Malekzadeh, Digestive Disease Research Centre, Tehran University of Medical Sciences, Tehran 14117-13135, Iran
Safa Najafi, Ardeshir Ghavamzadeh, Hematology, Oncology, BMT research Center, Tehran University of Medical Sciences, Tehran 14117-13135, Iran
Seyed Mohamad Tavangar, Department of Pathology, School of Medicine, Tehran University of Medical Sciences, Tehran 14117-13135, Iran
Author contributions: Zamani F and Mohamadnejad M participated in conception, design, undertaking of the study and manuscript writing; Shakeri R and Amiri A participated in data collection, data analysis and manuscript writing; Malekzadeh R participated in conception and experimental design of study. Other authors participated in data collection.
Supported by Local funds from Digestive Disease Research Centre, University of Tehran and Gastrointestinal and Liver Disease Research Centre, Iran University of Medical Science
Correspondence to: Reza Malekzadeh, Professor, Digestive Disease Research Center, Shariati Hospital, North Kargar Ave, Tehran 14117-13135, Iran. malek@ams.ac.ir
Telephone: +98-21-88012992 Fax: +98-21-88012992
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Abstract

AIM: To determine the prevalence of gluten sensitive enteropathy (GSE) in a large group of patients with iron deficiency anemia (IDA) of obscure origin.

METHODS: In this cross-sectional study, patients with IDA of obscure origin were screened for GSE. Anti-endomysial antibody (EMA) and tissue transglutaminase antibody (tTG) levels were evaluated and duodenal biopsies were taken and scored according to the Marsh classification. The diagnosis of GSE was based on a positive serological test and abnormal duodenal histology. Gluten free diet (GFD) was advised for all the GSE patients.

RESULTS: Of the 4120 IDA patients referred to our Hematology departments, 206 (95 male) patients were found to have IDA of obscure origin. Thirty out of 206 patients (14.6%) had GSE. The mean age of GSE patients was 34.6 ± 17.03 (range 10-72 years). The female to male ratio was 1.3:1. Sixteen patients had Marsh 3, 12 had Marsh 2, and 2 had Marsh 1 lesions. The severity of anemia was in parallel with the severity of duodenal lesions. Twenty-two GSE patients (73.3%) had no gastrointestinal symptoms. Fourteen GSE patients who adhered to GFD without receiving iron supplementation agreed to undergo follow up visits. After 6 mo of GFD, their mean hemoglobin levels (Hb) increased from 9.9 ± 1.6 to 12.8 ± 1.0 g/dL ($P < 0.01$). Interestingly, in 6 out of 14 patients who had Marsh 1/2 lesions (e.g. no villous atrophy) on duodenal biopsy, mean Hb increased from 11.0 ± 1.1 to 13.1 ± 1.0 g/dL ($P < 0.01$) while they did not receive any iron supplementation.

CONCLUSION: There is a high prevalence (e.g. 14.6%) of GSE in patients with IDA of obscure origin. Gluten free diet can improve anemia in GSE patients who have mild duodenal lesions without villous atrophy.

Key words: Gluten sensitive enteropathy; Iron deficiency anemia; Anti-Tissue transglutaminase antibody; Anti-endomysial antibody; Gluten free diet

Peer reviewer: Ioannis E Koutroubakis, MD, PhD, Assistant Professor of Medicine, University Hospital Heraklion, Department of Gastroenterology, PO Box 1352, 71110 Heraklion, Crete, Greece

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INTRODUCTION

Gluten sensitive enteropathy (GSE) is an autoimmune enteropathy due to food gluten intolerance in genetically predisposed people[1]. While GSE was thought to be a rare disease in the past and was believed to be essentially a disease of Europeans[2-5], recent screening studies showed that GSE is one of the most frequent genetically based diseases which occurs worldwide, with a prevalence ranging from 1:85 to 1:500 in different populations[6-9].

Several categories of GSE have recently emerged, including: monosymptomatic, oligosymptomatic, atypical (without gastrointestinal symptoms), silent, potential and latent form[10,11]. Iron deficiency anemia (IDA) is a commonly observed sign in GSE and is the only abnormality in 40% of patients[12]. In fact, only a minority of GSE patients present with classical malabsorption symptoms of diarrhea and weight loss, whereas most patients have subclinical or silent forms in which IDA can be the sole presentation[13].

In an extensive evaluation of the gastrointestinal tract in patients with IDA in order to identify a source of bleeding, the origin of bleeding cannot be detected in a significant minority of patients. In some of these patients IDA could be the result of diseases that impair iron absorption in the absence of bleeding[14,15]. Gluten sensitive enteropathy is one of these disorders which causes chronic inflammation in the bowel surface, leading to infiltration of T-lymphocytes, hyperplasia of crypts, villous atrophy and reduction of the bowel absorption surface for various nutrients such as iron[16].

Considering the broad spectrum of clinical manifestations of GSE, including anemia, osteoporosis, dermatitis herpetiformis, neurologic disorders and life-threatening complications such as non Hodgkin's lymphoma, small intestinal adenocarcinoma, esophageal cancer, and melanoma, early diagnosis of GSE is essential[17-20].

The present study was conducted to estimate the prevalence of GSE in a large group of patients with IDA of unknown origin by use of two highly sensitive and specific serological tests. We also present the follow-up data of those GSE patients who adhered strictly to a GFD and agreed to undergo follow up visits.

MATERIALS AND METHODS

Subjects

In this prospective study we evaluated all 4120 patients with IDA referred to the Hematology departments of Shariati Hospital, and Firoozgar Hospital from April 2003 to September 2007. Iron deficiency anemia was defined as: hemoglobin concentration less than 13.5 g/dL in men and less than 11.5 g/dL in women; mean corpuscular volume (MCV) less than 80 fl; and ferritin level less than 30 ng/mL.

Methods

Patients were evaluated in 6 steps. In step 1, patients with the following conditions were excluded from the study: known malignancies, hematological diseases (hemolytic anemia, aplastic anemia, thalassemia and myelodysplasia), known chronic diseases (e.g. chronic renal failure, chronic infectious disease, severe cardiac and respiratory disease, collagen vascular disease and chronic liver disease), pregnancy, heavy menstrual flow (cycles $\geqslant$ 7 d), menometrorrhagia, drug addiction, alcoholism, gastric surgery, and obvious blood loss (e.g. melena, hematochezia, hematuria, recurrent epistaxis). In this step 3559 patients were excluded and 561 were entered into the next step.

In step 2, patients were offered the chance to participate in the study, and a questionnaire was completed by each patient. Ninety-four patients declined to enter the study, and 467 patients entered into the next step. Informed consent was obtained from each patient and documented under institutional guidelines and oversight.

In step 3 all patients underwent colonoscopy. Patients with likely sources of blood loss, including any mass lesions, polyps greater than 1.5 cm, five or more vascular ectasias, histologically-proven inflammatory bowel disease, ischemic colitis, or solitary rectal ulcer were excluded. In this step 108 patients were excluded, and 359 patients were entered into the fourth step.

In step 4, all remaining patients underwent upper gastrointestinal endoscopy to exclude sources of blood loss, including varices, peptic ulcer, mass lesions, polyps greater than 1.5 cm in diameter, five or more vascular ectasias, or erosive gastritis. If none of the above lesions were detected, three biopsy specimens were taken from the second part of the duodenum. One hundred and forty seven patients were excluded in step 4.

In step 5, the remaining 212 patients underwent small bowel barium study. Six patients with abnormal small bowel series were excluded in this step.

Thus, from the 4120 patients with IDA who entered the Hematology department, 206 patients were found to have IDA of obscure origin.

In step 6, venous blood samples for tissue transglutaminase antibody (tTG) and endomysial antibody (EMA) were obtained from the 206 remaining patients with IDA of obscure origin. The duodenal biopsy specimens were fixed immediately in formalin solution for 4-8 h at room temperature and were routinely processed for conventional histological evaluation. The biopsy specimens were read by one expert histopathologist and the histological damage of duodenum was expressed based on Modified Marsh classification[3]: 0: Normal mucosal structure without significant lymphocytic infiltration; 1: Lymphocytic enteritis (more than 30 lymphocytes/100 epithelial cells); 2: Lymphocytic enteritis and crypt hyperplasia; 3A: Partial villous atrophy; 3B: Subtotal villous atrophy.

The levels of antibodies against IgA tTG were determined by ELISA using human recombinant tTG as the antigen (Orgentec Diagnostika GmbH, Mainz, Germany). Serum samples were diluted to 1:100 with distilled water, incubated with antigen for 30 min at room temperature, washed three times, and subsequently incubated for another 30 min with antihuman IgA. Optical density was read at 450 nm. Results were expressed in arbitrary units (AU) according to the reference calibrator. The cut-off value for a positive outcome was considered to be 10 AU, according to the instructions on the kit. IgA EMA assay was performed using an indirect immunofluorescence technique. The result was considered positive when bright green reticular fluorescence of smooth muscle was detected by fluorescence microscopy. Total serum IgA was measured in patients with negative tTG and EMA results to exclude IgA deficiency as a cause of false-negative tTG and EMA.

Table 1 Hemoglobin (Hb), Mean Corpuscular Volume (MCV) and Ferritin in GSE patients as compared with other anemic patients

	GSE	Other IDA patients[1]
Hb (g/dL)	9.8 ± 1.7	9.3 ± 2.0
MCV	74.0 ± 9.2	69.1 ± 12.6
Ferritin (ng/mL)	12.4 ± 9.8	11.2 ± 24.2

[1]*P* value was not significant compared to GSE patients (independent *t*-test).

Table 2 Mean hemoglobin level among patients with various degrees of duodenal lesions

MARSH classification	No. of GSE patients	Mean Hemoglobin level
1	2	11.2 ± 1.6
2	12	10.9 ± 1.2[b]
3	16	8.68 ± 1.5[b,d]

[b]*P* < 0.001 compared to Marsh 1 group (independent t-test), [d]*P* < 0.001 compared to Marsh 2 group (independent *t*-test).

The presence of positive tTG or EMA plus abnormal duodenal histology (e.g. Marsh 1, 2 or 3) was defined as gluten sensitivity enteropathy (GSE). All GSE patients were referred to our nutrition clinic and advised to follow a strict gluten free diet, but iron supplementation was withheld. Patients were followed up after 6 mo. Adherence to GFD was assessed in the follow up visit.

Statistical analysis

Data are presented as mean ± SD or percentage. Statistical analysis was performed using SPSS software version 15 and *t*-test for comparison of the means of quantitative variables. $P < 0.05$ was considered statistically significant.

RESULTS

From the 206 patients with IDA of obscure origin, 95 were men with a mean age of 37.6 ± 19.8 years, and 111 were women with a mean age of 39.1 ± 14.4 years.

Serological findings

Serological screening tests showed 31 patients had one or two positive tests. Twenty eight patients had positive tTG, and 23 had positive EMA. In 20 patients both tests were positive. None of the patients with negative serological tests was IgA-deficient.

Biopsy findings

Thirty-eight patients had abnormal duodenal histology. Sixteen patients had Marsh 3, 15 had Marsh 2 and 7 had Marsh 1. Among 38 patients with abnormal duodenal histology, 8 patients (3 with Marsh 2, and 5 with Marsh 1) had negative serologic tests. Eight patients who had abnormal duodenal histology but negative serological tests were not considered to have GSE.

GSE patients

Thirty out of 206 (14.6%) of the patients had GSE. The mean age of these patients was 34.6 ± 17.03 (range 10-72 years). The female/male ratio was 1.3:1. Thirty-one patients were positive for one or two serologic tests, but one of the tTG-positive patients had normal duodenal histology. Among 30 GSE patients, three had negative tTG, and seven had negative EMA. The mean duration of anemia before the diagnosis of GSE was 3.6 ± 1.4 years. These patients had been treated with oral iron for a mean duration of 1.9 years. Anemia improved in only 8 patients (26.8%) treated with oral iron supplementation before GSE diagnosis. Four patients (13.3%) had a family history of prolonged anemia of unknown cause in first degree relatives.

Six patients (20%) mentioned flatulence, two (6.7%) had intermittent diarrhea and one (3.3%) had dermatitis herpetiformis. There were no gastrointestinal symptoms in 22 GSE patients (73.3%).

The mean age of the GSE patients was not significantly different from other IDA of obscure origin patients (34.6 ± 17.0 *vs* 39.3 ± 17.1 years, respectively).

In Table 1, mean Hb, MCV and ferritin in GSE patients are compared with other patients with IDA of obscure origin. There were no statistically significant differences between the patient groups.

In GSE patients, the decrement in hemoglobin level was parallel to the severity of duodenal lesion. Patients with Marsh 3 lesions had more severe anemia (Table 2).

Sensitivity and specificity of the serologic tests

We calculated the sensitivity and specificity of the serological tests based on our definition of GSE (e.g. positive tTG or EMA, plus abnormal duodenal histology). The sensitivity and specificity of IgA tTG-Ab for diagnosing GSE were 90% and 98.5% respectively. Also, the sensitivity and specificity of EMA for diagnosing GSE were 76.6% and 100%, respectively.

Follow up

All the GSE patients were referred to our Nutrition Clinic, and GFD was advised for all of them. Iron supplementation was not started in the patients. The patients were invited for a follow up visit 6 mo after the diagnosis.

Four GSE patients were lost to follow up. Seven patients did not strictly adhere to GFD. For five other patients, iron supplementation was started at other clinics during the follow up period. Thus, we present the follow up data of 14 patients who strictly adhered to GFD and did not use iron supplementation during the 6 mo follow up period.

Mean hemoglobin increased from 9.9 ± 1.6 to 12.8 ± 1.0 g/dL ($P < 0.001$), and mean serum ferritin level increased from 12.0 ± 6.0 to 22.1 ± 7.9 ng/mL.

Interestingly, in 6 patients with Marsh 1/2 lesions (e.g. without villous atrophy) mean Hb increased from 11.0 ± 1.1 to 13.1 ± 1.0 g/dL ($P = 0.002$), and mean serum ferritin level increased from 16.5 ± 4.3 to 25.9 ± 6.2 ng/ml ($P = 0.014$). Demographic and clinical data are presented in Table 3.

Table 3 Demographic and clinical data of the 6 patients with Marsh 1/2 lesions that adhered to GFD

Patient No.	Gender	Age	Marsh classification	Hb level before GFD (g/dL)	Hb level 6 mo after GFD (g/dL)	Ferritin level before GFD (ng/mL)	Ferritin level 6 mo after GFD (ng/mL)
1	Male	29	1	12.8	14.0	19	24.6
2	Male	10	2	10.5	13.5	13.7	34.0
3	Female	17	2	9.5	12.2	20	23.5
4	Male	22	2	11.5	13.0	18	31.0
5	Male	30	2	11.1	14.2	9	16.2
6	Female	38	2	10.4	11.8	19	26.0

DISCUSSION

In this prospective study, we found GSE as the cause of IDA of obscure origin in a significant proportion (14.6%) of patients. Various rates of prevalence of GSE in IDA patients have been reported among different studies[21-24]. This discrepancy may be explained by patient selection criteria in the different studies.

In our study, the prevalence of GSE is amongst the highest rates reported. One reason is that we evaluated GSE among highly selected patients in whom the cause of IDA could not be identified after extensive evaluation. Also, we considered patients with positive serological tests and milder degrees of duodenal mucosal lesions (e.g. Marsh 1 or 2) as having GSE.

Physicians may fail to consider GSE as a cause of IDA when gastrointestinal symptoms are absent or nonspecific. In this study, most GSE patients (73.3%) did not report any gastrointestinal symptoms. In our study, there were no differences in demographic characteristics or hematological indices between GSE patients and other patients with anemia of obscure origin to help to distinguish them (Table 1). In GSE patents, the hemoglobin level was inversely correlated with the severity of the histological injury. Patients with Marsh 3 lesions had the most severe anemia, consistent with the role of impaired intestinal absorption in the pathogenesis of IDA. We found marked improvement of anemia in 14 patients who adhered to GFD but did not use iron supplementation. Many authors consider the presence of villous atrophy (e.g. Marsh 3) as one of the major criteria for diagnosing celiac disease (CD)[25,26]. In order to avoid this controversy in the definition of CD, we used the term "gluten sensitive enteropathy" rather than celiac disease to describe patients with any degree of intestinal damage together with positive serologic tests. In this study, we showed a significant objective improvement in hemoglobin level with GFD alone in patients with positive serology but no villous atrophy (e.g. Marsh 1 or 2). Our study suggests that restriction of the diagnosis of CD to patients with overt villous atrophy will exclude some patients who might benefit from GFD.

In this study, we used a human recombinant protein-based tTG test, which has higher sensitivity and accuracy than a guinea pig protein-based tTG test[27]. However, neither tTG nor EMA was 100% sensitive. We found 7 patients with positive tTG, negative EMA and intestinal damage. On the other hand, we found 3 patients with negative tTG, positive EMA, and duodenal lesions. While some guidelines suggest that either EMA or tTG is sufficient for identifying patients with CD[27,28], our study provides evidence that both tTG and EMA should be used for diagnosing CD.

In this study we did not evaluate GSE in all patients with IDA. One may speculate that some patients who were excluded before step 5, may have had GSE as well as another cause of IDA. The prevalence of GSE in IDA has been reported in previous studies[21-23]. In fact, the aim of our study was to evaluate GSE in a large population of patients with IDA of obscure origin. In a population based study done in Iran, the female to male ratio of GSE was 1 to 1.1[9]. Thus, the female to male ratio found in our study represents the ratio of the disease found in the general population of the country.

In conclusion, celiac disease should be considered in any patient with unexplained IDA, even if they do not have any gastrointestinal symptoms. Furthermore, GFD can improve anemia in IDA patients who have positive tTG/EMA and mild duodenal lesions without villous atrophy.

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COMMENTS

Background

Iron deficiency anemia (IDA) is the only abnormality in 40% of patients diagnosed with gluten sensitive enteropathy (GSE). The majority of patients with GSE don't present with classical malabsorption symptoms such as diarrhea and weight loss. In this study we determined the prevalence of GSE in patients with IDA in Iran.

Research frontiers

Recent screening studies shows that GSE is one of the most commongenetic based diseases which occurs worldwide, with a prevalence of ranging from 1:85 to 1:500 in different populations. Various rates of prevalence of GSE in IDA patients have been reported among different studies probably due to different patient selection criteria in these studies.

Innovation and breakthroughs

Iron deficiency anemia is a common presentation of GSE and can be the sole presentation of the disease. Gluten free diet (GFD) might improve mild duodenal damage (e.g. Marsh 1 or 2) without villous atrophy.

Applications

According to our results, identification of anemic patients with underlying GSE is of great importance. Since IDA can be the sole manifestation of GSE, by diagnosing GSE and giving GFD to patients, we can both prevent the complications of GSE and probably cure IDA without iron supplementation.

Terminology

GSE is an autoimmune enteropathy triggered by the ingestion of gluten-containing grains in susceptible individuals.

Peer review

This is a well-written, well analyzed and scientifically accurate manuscript. The paper is balanced in every part, the reference list is adequate and the conclusions are clear.

REFERENCES

1 **Lima VM**, Gandolfi L, Pires JA, Pratesi R. Prevalence of celiac disease in dyspeptic patients. *Arq Gastroenterol* 2005;

42: 153-156
2 **Davidson LS**, Fountain JR. Incidence of the sprue syndrome; with some observations on the natural history. *Br Med J* 1950; **1**: 1157-1161
3 **Marsh MN**. The natural history of gluten sensitivity: defining, refining and re-defining. *QJM* 1995; **88**: 9-13
4 **Fasano A**, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001; **120**: 636-651
5 **Goggins M**, Kelleher D. Celiac disease and other nutrient related injuries to the gastrointestinal tract. *Am J Gastroenterol* 1994; **89**: S2-S17
6 **Kolho KL**, Farkkila MA, Savilahti E. Undiagnosed coeliac disease is common in Finnish adults. *Scand J Gastroenterol* 1998; **33**: 1280-1283
7 **Catassi C**, Fabiani E, Ratsch IM, Coppa GV, Giorgi PL, Pierdomenico R, Alessandrini S, Iwanejko G, Domenici R, Mei E, Miano A, Marani M, Bottaro G, Spina M, Dotti M, Montanelli A, Barbato M, Viola F, Lazzari R, Vallini M, Guariso G, Plebani M, Cataldo F, Traverso G, Ventura A. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatr Suppl* 1996; **412**: 29-35
8 **Accomando S**, Cataldo F. The global village of celiac disease. *Dig Liver Dis* 2004; **36**: 492-498
9 **Akbari MR**, Mohammadkhani A, Fakheri H, Javad Zahedi M, Shahbazkhani B, Nouraie M, Sotoudeh M, Shakeri R, Malekzadeh R. Screening of the adult population in Iran for coeliac disease: comparison of the tissue-transglutaminase antibody and anti-endomysial antibody tests. *Eur J Gastroenterol Hepatol* 2006; **18**: 1181-1186
10 **Martucci S**, Biagi F, Di Sabatino A, Corazza GR. Coeliac disease. *Dig Liver Dis* 2002; **34** Suppl 2: S150-S153
11 **Biagi F**, Corazza GR. Clinical features of coeliac disease. *Dig Liver Dis* 2002; **34**: 225-228
12 **Unsworth DJ**, Lock RJ, Harvey RF. Improving the diagnosis of coeliac disease in anaemic women. *Br J Haematol* 2000; **111**: 898-901
13 **Brandimarte G**, Tursi A, Giorgetti GM. Changing trends in clinical form of celiac disease. Which is now the main form of celiac disease in clinical practice? *Minerva Gastroenterol Dietol* 2002; **48**: 121-130
14 **Annibale B**, Capurso G, Chistolini A, D'Ambra G, DiGiulio E, Monarca B, DelleFave G. Gastrointestinal causes of refractory iron deficiency anemia in patients without gastrointestinal symptoms. *Am J Med* 2001; **111**: 439-445
15 **Rockey DC**, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. *N Engl J Med* 1993; **329**: 1691-1695
16 **Silano M**, Volta U, Mecchia AM, Dessi M, Di Benedetto R, De Vincenzi M. Delayed diagnosis of coeliac disease increases cancer risk. *BMC Gastroenterol* 2007; **7**: 8
17 **Hernandez L**, Green PH. Extraintestinal manifestations of celiac disease. *Curr Gastroenterol Rep* 2006; **8**: 383-389
18 **Somech R**, Spirer Z. Celiac disease: extraintestinal manifestations, associated diseases, and complications. *Adv Pediatr* 2002; **49**: 191-201
19 **Tursi A**, Giorgetti G, Brandimarte G, Rubino E, Lombardi D, Gasbarrini G. Prevalence and clinical presentation of subclinical/silent celiac disease in adults: an analysis on a 12-year observation. *Hepatogastroenterology* 2001; **48**: 462-464
20 **Green PH**, Fleischauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI. Risk of malignancy in patients with celiac disease. *Am J Med* 2003; **115**: 191-195
21 **Ackerman Z**, Eliakim R, Stalnikowicz R, Rachmilewitz D. Role of small bowel biopsy in the endoscopic evaluation of adults with iron deficiency anemia. *Am J Gastroenterol* 1996; **91**: 2099-2102
22 **Karnam US**, Felder LR, Raskin JB. Prevalence of occult celiac disease in patients with iron-deficiency anemia: a prospective study. *South Med J* 2004; **97**: 30-34
23 **Grisolano SW**, Oxentenko AS, Murray JA, Burgart LJ, Dierkhising RA, Alexander JA. The usefulness of routine small bowel biopsies in evaluation of iron deficiency anemia. *J Clin Gastroenterol* 2004; **38**: 756-760
24 **Patterson RN**, Johnston SD. Iron deficiency anaemia: are the British Society of Gastroenterology guidelines being adhered to? *Postgrad Med J* 2003; **79**: 226-228
25 **Feighery C**, Conlon N, Jackson J. Adult population screening for coeliac disease: comparison of tissue-transglutaminase antibody and anti-endomysial antibody tests. *Eur J Gastroenterol Hepatol* 2006; **18**: 1173-1175
26 **Abrams JA**, Brar P, Diamond B, Rotterdam H, Green PH. Utility in clinical practice of immunoglobulin a anti-tissue transglutaminase antibody for the diagnosis of celiac disease. *Clin Gastroenterol Hepatol* 2006; **4**: 726-730
27 **Hill ID**. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? *Gastroenterology* 2005; **128**: S25-S32
28 **James SP**. This month at the NIH: Final statement of NIH Consensus Conference on celiac disease. *Gastroenterology* 2005; **128**: 6

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