

Detection of Celiac Disease in Primary Care: A Multicenter Case-Finding Study in North America

Carlo Catassi, M.D., M.P.H.,¹ Deborah Kryszak, B.S.,¹ Otto Louis-Jacques, M.D.,¹ Donald R. Duerksen, M.D.,² Ivor Hill, M.D.,³ Sheila E. Crowe, M.D.,⁴ Andrew R. Brown, M.D.,⁴ Nicholas J. Procaccini, M.D.,⁴ Brigid A. Wonderly, R.N.,⁴ Paul Hartley, M.D.,⁵ James Moreci, M.D.,⁵ Nathan Bennett, M.D.,⁵ Karoly Horvath, M.D., Ph.D.,¹ Margaret Burk, R.N.,¹ and Alessio Fasano, M.D.¹
¹*Mucosal Biology Research Center and Division of Pediatric Gastroenterology and Nutrition, University of Maryland School of Medicine, Baltimore, Maryland;* ²*Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada;* ³*Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, North Carolina;* ⁴*Department of Internal Medicine, University of Virginia Health System, Charlottesville, Virginia;* and ⁵*Preferred Primary Care Physicians, Pittsburgh, Pennsylvania*

BACKGROUND: Celiac disease (CD) is one of the most common lifelong disorders in western countries. However, most cases remain currently undiagnosed in North America, mostly due to poor awareness of CD by primary care physicians.

OBJECTIVES: The aims of this study were (a) to determine whether an active case-finding strategy in primary care could increase the frequency of CD diagnosis and (b) to determine the most common clinical presentations of the condition.

METHODS: This was a multicenter, prospective study involving adult subjects during the years 2002–2004, attending one of the participating practices. All individuals with symptoms or conditions known to be associated with CD were tested for immunoglobulin A anti-transglutaminase (tTG) antibodies, and those with elevated anti-tTG were subsequently tested for IgA antiendomysial antibodies (EMA). All subjects who were positive for EMA were advised to undergo an intestinal biopsy and HLA typing.

RESULTS: The study group included 737 women and 239 men, with a median age of 54.3 yr. A positive anti-tTG test was found in 30 out of 976 investigated subjects (3.07%, 95% CI 1.98–4.16). CD was diagnosed in 22 patients (18 women, 4 men). The most frequent reasons for CD screening in these 22 cases were bloating (12/22), thyroid disease (11/22), irritable bowel syndrome (7/22), unexplained chronic diarrhea (6/22), chronic fatigue (5/22), and constipation (4/22). The prevalence of CD in the serologically screened sample was 2.25% (95% CI 1.32–3.18). The diagnostic rate was low at baseline (0.27 cases per thousand visits, 95% CI 0.13–0.41) and significantly increased to 11.6 per thousand visits (95% CI 6.8–16.4, $P < 0.001$) following active screening implementation.

CONCLUSIONS: This study demonstrates that an active case-finding strategy in the primary care setting is an effective means to improve the diagnostic rate of CD in North America.

(Am J Gastroenterol 2007;102:1–7)

INTRODUCTION

Celiac disease (CD) is an immune-mediated enteropathy caused by the ingestion of gluten-containing cereals (wheat, rye, and barley) in genetically predisposed individuals. In countries where most people are of European ancestry, CD is one of the most common lifelong disorders (1). Recent epidemiological surveys in Europe and in the United States of America showed the prevalence of CD in the general population is between 0.5 and 1% (2). Many cases remain undiagnosed, usually because they have atypical symptoms and because there is a lack of awareness of CD by doctors. In a

large European survey, the ratio between diagnosed and undiagnosed cases (the latter found by mass serological screening) was as high as 1 to 7 (the so called “celiac iceberg”) (3). In addition to having chronic symptoms that might otherwise respond to a gluten-free diet (GFD), undiagnosed patients are exposed to the risk of long-term complications of CD, such as anemia, infertility, osteoporosis, or cancer (especially intestinal lymphoma).

The diagnosis of CD is based on finding the characteristic histological features on small intestinal biopsy and a clinical response to the GFD. However, serological markers, e.g., the IgA class anti-tissue transglutaminase (tTG) antibodies,

are useful screening tests. The sensitivity and the specificity of the IgA anti-tTG test are 94% and 97%, respectively (4). Serological screening of the general population will identify most cases of previously unrecognized CD, but mass screening for CD is not currently recommended, as the potential cost/benefits of such a strategy have not been determined. An active case-finding strategy targeting both symptomatic and asymptomatic individuals who are at risk for CD is currently considered a more cost-effective approach to diagnosis (5). The case-finding strategy has the following advantages compared with mass screening: (a) selective finding of subjects with health problems and poor quality of life, who can immediately benefit from treatment with a GFD, and (b) it is less expensive (6).

The level of awareness of CD and its clinical polymorphism is low in the United States of America, although it has increased recently (7). Serological testing for CD is currently not widely adopted by primary care physicians. In a recent nationwide study, a small bowel biopsy was not taken in the majority of patients (89%) undergoing gastroduodenoscopy because of possible symptoms of CD (anemia, iron deficiency, weight loss, or diarrhea) (8). Consequently, the majority of individuals with CD remain undiagnosed in the United States of America, with a calculated ratio of diagnosed to undiagnosed cases being as high as 1 to 50–100 (2).

A primary care practice provides the best opportunity to first identify individuals who are at risk for CD and need referral for definitive diagnosis. For this reason, we undertook a multicenter, prospective, case-finding study using serological testing of adults who were seeking medical attention from their primary care physician in the United States of America and Canada. The aims of this study were (a) to determine whether an active case-finding strategy could increase the frequency of CD diagnosis and (b) to determine the most common clinical presentations of the condition in this setting.

PATIENTS AND METHODS

This was a multicenter, prospective study involving adult subjects during the years 2002–2004, attending one of the participating community-based or university-based internal medicine or family practices. During the days of patient recruitment, any individual over the age of 18 yr seeking care from their physician was informed of the study by reception staff. Those willing to participate in the study completed a questionnaire and anyone indicating the presence of one or more of the items listed in Table 1 was considered at risk for CD and therefore eligible for the study. All at-risk individuals were provided detailed information about CD and were offered free serological testing. Participants agreeing to have blood drawn were first tested for immunoglobulin A anti-tTG antibodies and those with elevated anti-tTG were subsequently tested for serum IgA class antiendomysial antibodies (EMA) to improve the specificity of the screening process (9). All subjects who were positive for EMA were advised to undergo an intestinal biopsy and HLA typing for detec-

Table 1. Criteria for Enrolment of Patients

Family history of CD (first- or second-degree relative)
Unexplained anemia or iron deficiency
Recurrent abdominal pain or bloating
Irritable bowel syndrome or chronic diarrhea (longer than 2 wk)
Chronic fatigue
Abnormal liver function test (AST, ALT)
Autoimmune disorders, <i>e.g.</i> , type 1 diabetes, thyroiditis, autoimmune hepatitis, rheumatoid arthritis or other connective tissue disease vitiligo, Sjogren's syndrome
Down's syndrome
Turner's syndrome
Infertility
Epilepsy or ataxia

tion of CD-predisposing genotypes, for definitive diagnosis of CD. Small intestinal biopsies were centrally reviewed and the histological findings were graded according to the Marsh classification modified by Oberhuber *et al.* (10).

Individuals with selective IgA deficiency (SIgAD: total serum IgA lower than 5 mg %) have a greater risk of CD, but may be missed by these IgA-based screening tests. These individuals typically have very low values of IgA anti-tTG (<0.5 arbitrary units, AU) (11). Therefore, in individuals with low IgA anti-tTG, total serum IgA level was determined by using the previously collected serum. Those with SIgAD were then tested with IgG anti-human tTG. A small intestinal biopsy and HLA typing were also recommended for those with SIgAD and IgG anti-h-tTG higher than 26.0 AU.

The number of cases of CD diagnosed during the year prior to initiation of this case-finding study was retrospectively obtained from record reviews of participating practices.

Anti-tTG antibodies were measured using an ELISA method based on human recombinant antigen. A value higher than 7.0 AU for IgA and 26.0 AU for IgG was considered positive. EMA was detected by indirect immunofluorescence, using monkey esophagus as the substrate, and a value above 1:4 was considered as positive. Both tests were centrally performed at the coordinating site (University of Maryland, Center for Celiac Research) using commercial assays provided by SciMedX (Denville, NJ).

Genomic DNA extraction was performed using the QIAamp® DNA Blood Kit (QIAGEN® Inc., Valencia, CA). HLA typing was centrally performed at the coordinating site using the Eu-DQ® Kit (Eurospital, Trieste, Italy) to detect the heterodimer DQ2 and DQ8 haplotypes, respectively, codified by alleles DQA1*0501, DQB1*02, and DQB1*0302. The kit is composed of two multiplex PCR reactions: one with DQA1*0501-DQB1*0302 primers, the second with DQB1*02. Both use beta-globin primers as internal control. The amplicons obtained are resolved on 2% agarose gel and stained using ethidium bromide in the electrophoresis analysis.

Case Definition

For the purpose of this study, a diagnosis of CD was considered positive in patients fulfilling at least one of the following criteria: (a) a positive IgA anti-tTG and EMA together

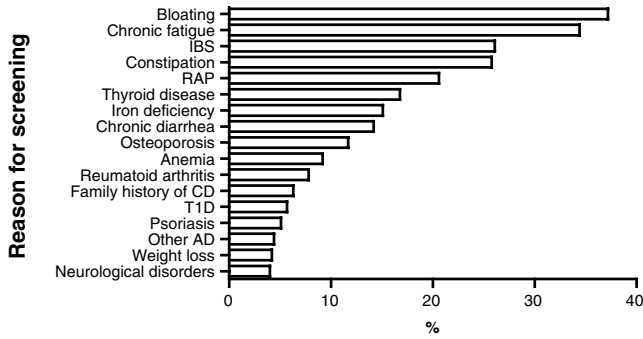


Figure 1. Prevalence of symptoms and/or conditions associated with the CD screening. IBS = irritable bowel syndrome; RAP = recurrent abdominal pain; T1D = type 1 diabetes; AD = autoimmune disease.

with features of mucosal changes on small intestinal biopsy (ranging from isolated increase of the intraepithelial lymphocyte count [grade 1 lesion] to villous atrophy [grade 3 lesion]); (b) a positive test for both IgA anti-tTG and EMA plus HLA typing compatible with the diagnosis of CD (HLA-DQ2 and/or DQ8 positive) in those refusing an intestinal biopsy; (c) a positive test for IgG class anti-tTG antibodies in subjects with SIgAD plus HLA typing compatible with the diagnosis of CD (HLA-DQ2 and/or DQ8 positive).

All those with a positive diagnosis of CD were advised to go onto a strict GFD.

The Institutional Review Board (IRB) of the University of Maryland approved this study protocol. Approval was also obtained by the local IRB of participating sites.

Statistical Analysis

Data are presented as absolute numbers and percentages. The incidence rate and the prevalence of CD are expressed as mean value and 95% confidence interval (CI).

RESULTS

Overall 2,568 patients were interviewed for participation. Eight hundred fifty-nine out of 2,568 (33.5%) were asked but did not qualify for the study, 67 (2.6%) were asked but declined the questionnaire, 666 (25.9%) were eligible for the study but refused the serological screening test, and 976 (38.0%) were eligible and enrolled in the study.

The study group included 737 women and 239 men, with a median age of 54.3 yr, 105 (10.8%) were 18–30 yr old, 147 (15.1%) were 31–40, 181 (18.5%) were 41–50, 175 (17.9%) were 51–60, 142 (14.5%) were 61–70, 133 (13.6%) were 71–80, 79 (8.1%) were 81–90, 12 (1.2%) were 90 and older, and 2 (0.2%) unknown. The ethnic background of study participants was white (88.7%), African American (4.8%), American Indian (1.0%), Asian (0.5%), Latino (0.2%), native Hawaiian (0.1%), unknown or declined (4.7%). Figure 1 shows the prevalence of symptoms and/or conditions associated with the CD screening. In some cases, individuals had more than one reason for undergoing serological testing for CD. Figure 2 shows the results of the CD screening in the 976 enrolled patients. A positive IgA anti-tTG test was found in 30 out of 976 investigated patients (3.07%, 95% CI 1.98–4.16).

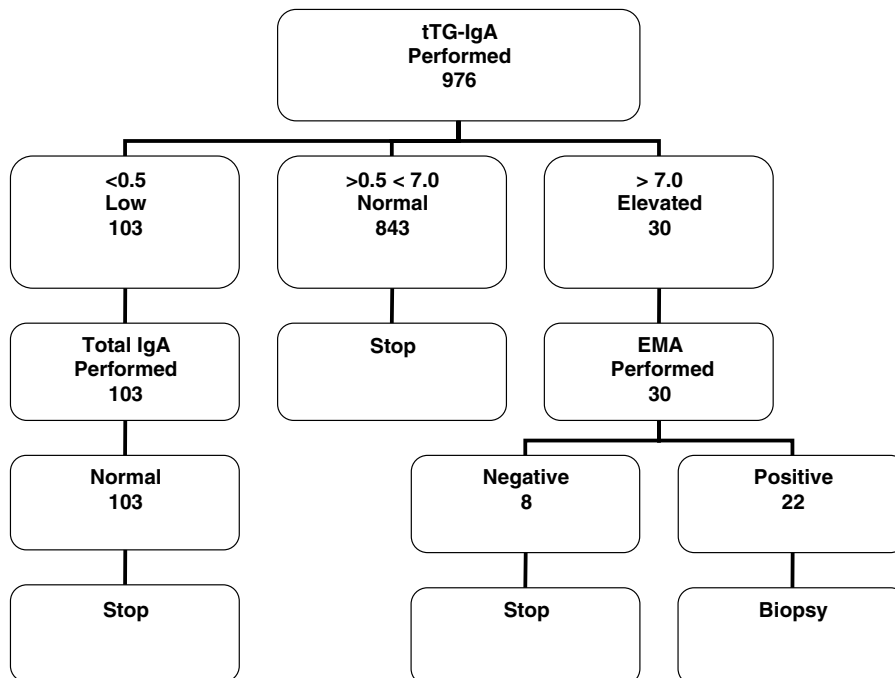


Figure 2. Results of the celiac screening in the 976 enrolled patients.

Table 2. Clinical Features of Newly Diagnosed Cases of CD

Case	Gender	Age	Symptoms/Disease		Anti-tTG	HLA	SI Biopsy	GFD
			Duration	Clinical Findings				
1	F	48	3–10 yr	Thyroid disease	7.9	DQ2	Refused	No
2	F	65	> 10 yr	Iron deficiency	18.3	DQ2	n.a.	n.a.
3	M	56	1–3 yr	IBS	9.4	DQ2	3B	No
4	F	46	1–3 yr	T1D, IBS	21.1	DQ2	3C	Yes
5	F	57	1–3 months	Chronic diarrhea	22.1	DQ2	3C	Yes
6	F	33	1–3 months	RAP, bloating	12.8	DQ2	n.a.	No
7	F	54	3–10 yr	Thyroid disease, infertility, IBS	25.4	DQ2	3B	Yes
8	F	35	> 10 yr	Down's, thyroid disease	20.2	DQ2	Refused	Yes
9	F	35	3–10 yr	Thyroid disease	17.3	DQ2	3A	Yes
10	F	54	4–10 days	Bloating	14.8	DQ2	3C	Yes
11	M	74	3–10 yr	IBS	12.5	DQ2	3A	Yes
12	F	45	1–3 yr	Bloating	17.6	DQ2	n.a.	n.a.
13	F	19	> 10 yr	Family history	13.7	DQ2/DQ8	n.a.	Yes
14	F	47	> 10 yr	Iron deficiency, IBS	20.3	DQ2	3A	Yes
15	F	62	1–3 yr	IBS, RA, RAS	19.6	DQ2	3C	Yes
16	F	35	> 10 yr	IBS, RAS	17.6	DQ2	3A	Yes
17	F	51	> 10 yr	Iron deficiency	11.9	DQ2	3A	Yes
18	F	25	3–12 months	Thyroid disease	19.6	DQ2	3A	Yes
19	F	75	1–3 yr	Family history, IBS, RA	18.9	DQ2	3A	Yes
20	F	49	3–10 yr	Thyroid disease, IBS	19.2	n.d.	3B	Yes
21	M	83	1–3 yr	Thyroid disease	19	DQ2	refused	Yes
22	M	34	3–10 yr	IBS	16.6	DQ2	3C	Yes

IBS = irritable bowel syndrome; T1D = type 1 diabetes; RAP = recurrent abdominal pain; RA = rheumatoid arthritis; RAS = recurrent aphthous stomatitis; n.a. = not available; n.d. = not done.

CD was diagnosed in 22 out of 976 investigated patients (18 women, 4 men). Table 2 shows the clinical features of these 22 cases. The most frequent reasons for CD screening in these 22 cases were bloating (12/22), thyroid disease (11/22), irritable bowel syndrome (IBS) (7/22), unexplained chronic diarrhea (6/22), chronic fatigue (5/22), and constipation (4/22). Figure 3 shows the prevalence of CD in each at-risk subgroup of investigated patients. The small bowel biopsy was available in 15 out of 22 patients and the GFD was implemented in 17 out of 22 cases. The prevalence of CD in the overall screened sample was 2.25% (95% CI 1.32–3.18). The prevalence of CD according to age was 2.78%

(95% CI 0.75–4.81) in subjects 40 yr old or younger, 2.81 (95% CI 1.10–4.52) in subjects age 41–60, and 1.37 (95% CI 0.18–2.56) in subjects older than 60.

During the 12 months preceding this study, only 15 patients had been diagnosed with CD out of 54,988 individuals seen by the participating practices (0.27 cases per thousand visits, 95% CI 0.13–0.41). During the study period, the diagnostic rate significantly increased to 8.6 per thousand visits (95% CI 5.0–12.1, $P < 0.001$) and to 11.6 per thousand visits (95% CI 6.8–16.4, $P < 0.001$), calculated on either 2,568 subjects (overall study population) or 1,902 subjects (excluding the 666 individuals that were eligible for the study but refused the serological screening test).

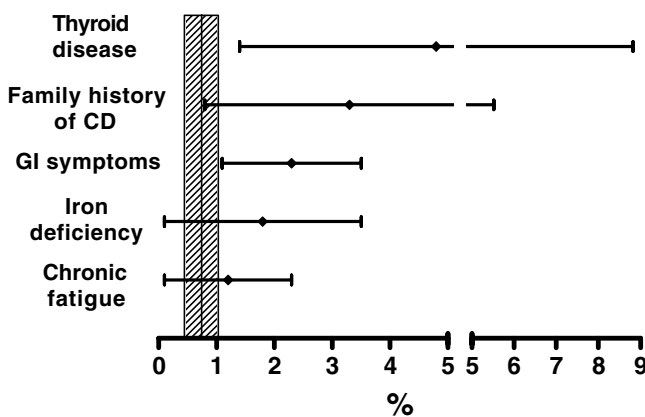


Figure 3. Prevalence of CD (and 95% CI) in selected at-risk subgroup of investigated patients. The dotted area is the prevalence of CD in the general U.S. population (2). GI = gastrointestinal.

DISCUSSION

Recent studies involving both the general population and at-risk groups have demonstrated that CD is one of the most common lifelong disorders in North America, and have resulted in greater interest in this condition (2, 12, 13). In a large sample of the general population in the United States of America, CD prevalence was estimated to be 1 in 133 subjects, a figure that is similar to that in many other studies performed in Europe. According to this estimate, the projected number of individuals with CD in the United States of America could be as high as three million, yet only a small fraction of these cases has been correctly diagnosed and treated. Recently, Murray *et al.* reported an increase in the annual incidence rate of newly diagnosed CD cases in Olmsted County, Minnesota, from 3.3 per 100,000 during the 1990s to 9.1 per 100,000 during the years 2000–2001 (7).

However, this rate is still lower than reported in Europe during the same period of time (17 per 100,000) (14). In order to improve awareness, diagnosis, and management of CD, the National Institutes of Health (NIH) convened a Consensus Development Conference on Celiac Disease on June 28–30, 2004 (15).

Our case-finding study included screening of asymptomatic patients running a greater risk of CD, *e.g.*, some of the subjects with either type 1 diabetes or family history of CD. This is still a controversial issue, as the long-term benefits of early detection and treatment with a GFD are not proven (16, 17). We decided to include apparently asymptomatic cases for several reasons: (a) patients with clinically silent CD may actually experience subtle and/or unrecognized symptoms, including change in behavior that may negatively impact the psycho-physical well-being, *e.g.*, by contributing to underachievement in education or working life (18) or to osteopenia (19); (b) patients with apparently silent disease may develop symptoms later in life (20); (c) individuals with undiagnosed CD may carry the risk of greater mortality (21).

The serum IgA anti-tTG test was used for first-level screening of CD because it is an accurate, easy to perform, and operator-independent test (17). However, we chose to restrict our analysis to those positive to both anti-tTG and EMA because there is evidence in the literature suggesting a higher positive predictive value of the EMA as compared with the anti-tTG test (9, 22). While we do not suggest that IgA anti-tTG lacks specificity, we elected to be conservative in recommending a small intestinal biopsy to those patients that tested positive in both tests.

Our data indicate that CD is still largely underdiagnosed in North America at the primary care level. By applying simple and well-established criteria for CD case finding on a sample of adults, we achieved a 32- to 43-fold increase in the diagnostic rate of this condition. This is a conservative estimate, as more CD cases could have been detected among the 666 individuals that were eligible for the study but refused the serological screening test. The markedly higher proportion of women among the newly diagnosed cases (18 out of 22) is in line with the results of previous European case-finding studies on CD (23, 24). This finding reflects the well-known higher rate of primary care consultation by women (25), but can also be explained by the gender distribution of some entry criteria (*e.g.*, thyroid disorders are more common in women) and by the higher prevalence of CD in women than in men (1). Not surprisingly, the 2.3% prevalence of CD in this selected, at-risk study group was higher than that of the general population in the United States of America (0.75%) (2), but is not much different from that found by Hin and coworkers in their pilot case-finding study in the U.K. (3%) (26). These prevalence figures are also very similar to those from a recent case-finding study targeting at-risk groups of children in the United States of America (27). Many newly diagnosed cases of CD reported a long-standing history of symptoms (usually of years) that should have raised the suspicion of CD well before (Table 2). This finding is in keeping with the results of a recent survey among adult celiacs in New York,

showing that the mean diagnostic delay was as long as 5.8 ± 0.5 yr (28). The general lack of awareness of the variable CD clinical manifestations and disease associations was recently highlighted in a survey of 132 primary care physicians in a southern California county. Although doctors surveyed had been in medical practice for an average of 20 yr, only 35% had ever diagnosed a patient with CD (29). The unfavorable environment for CD diagnosis in primary care is also reflected by the high proportion of patients in our study that were reluctant to complete the diagnostic workup with the small intestinal biopsy (7 out of 22 cases) or start treatment with the GFD (5 out of 22 cases).

In this study group, the most frequent risk factors for undiagnosed CD were: (a) thyroid disease, (b) positive family history of CD, (c) persistent gastrointestinal complaints, and (d) iron deficiency with or without anemia. The greater frequency of CD in several thyroid diseases (Hashimoto's thyroiditis, Grave's disease, and primary hypothyroidism) is well established (30); however, this disease association has received considerably less attention than other autoimmune disorders associated with the condition, *e.g.*, type 1 diabetes. A 3- to 5-fold increase in CD prevalence has been reported in subjects with autoimmune thyroid disease (31, 32). On the other hand, CD-associated hypothyroidism may sometimes lack features of an autoimmune process. Interestingly, treatment of CD by gluten withdrawal may lead to normalization of subclinical hypothyroidism (30). With respect to family history of CD, the high degree of familial clustering of CD, with about 10% of first-degree relatives being affected, is well known (33). A greater risk of CD has also been documented in second-degree relatives of CD patients (2). For this reason, family members showing HLA genotypes associated with CD (DQ2 and/or DQ8) should be screened by serological CD markers (*e.g.*, IgA anti-tTG) to rule out asymptomatic or atypical CD. The association of persistent intestinal complaints, *e.g.*, IBS-like symptoms, with CD is also well known. A systematic review of the literature showed that the pretest probability of CD in patients meeting symptom-based criteria for IBS is 10 times higher than in the general population (34). Furthermore, two different analyses have shown that testing for CD in patients with suspected IBS is likely to be cost-effective even at a low CD prevalence (3–8%) (35, 36). A large number of patients with newly diagnosed CD have iron-deficiency anemia (37). In a recent U.S. study, routine small bowel biopsy led to a diagnosis of CD in 8.7% of patients presenting with iron-deficiency anemia (38).

Selective IgA deficiency (SIgAD) occurs more commonly in patients with CD than in the general population (39). Patients with CD and SIgAD are missed by using the IgA anti-tTG test (or any other IgA-based test, *e.g.*, EMA) for screening purposes. To overcome this problem, it has been suggested that total IgA levels be measured in individuals who have very low levels of IgA anti-tTG (<0.5 U) on initial serological testing (11). The use of this two-step diagnostic approach in our study led to the determination of total IgA levels in 10.6% of screened samples without identifying a single case of SIgAD. Further studies are required to determine

the value of the SIgAD issue in CD screening (which is likely to be limited given the relative rarity of this association), as well as more cost-effective approaches to the diagnosis of SIgAD, *e.g.*, parallel determination of IgA and IgG anti-tTG or IgA anti-tTG and total IgA levels.

In conclusion, our study demonstrates that an active case-finding strategy in the primary care setting is an effective means to improve the diagnostic rate of CD in North America. The most common reasons for positive screening tests included gastrointestinal symptoms, thyroid disease, family history of CD, and iron deficiency. It is strongly recommended that all individuals be screened for the large variety of clinical manifestations and conditions associated with CD by their primary care physicians. Those with one or more of these features should have serological testing for CD and, if positive, should be referred for definitive diagnosis by means of an intestinal biopsy. A larger application of this protocol could raise the awareness and increase detection of this common disorder among primary care physicians and in the general population in North America.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Celiac disease (CD) is one of the most frequent chronic genetic disorders of humankind, affecting approximately 1% of the general population worldwide.
- The disease was previously considered to be confined to Europe.
- Recent epidemiological studies suggest that CD is also frequent in other countries, including the United States and Canada, where the overall prevalence in the general population is similar to that reported in Europe.
- These epidemiological studies also showed that the clinical presentation of the disease can be extremely variable, presenting with both intestinal and extraintestinal symptoms.

What Is New Here

- The level of awareness of the disease among health-care professional is still low. Therefore, the disease remains highly underdiagnosed in North America.
- Our studies showed that our active case-finding strategy increased the rate of diagnosis by primary care physicians by 32- to 43-fold.
- Patients experiencing both intestinal symptoms (diarrhea, irritable bowel syndrome, constipation, and bloating) and extraintestinal symptoms (thyroid diseases, iron deficient anemia, osteoporosis) are at higher risk for CD compared with the general population.
- Our results have implications that may resolve in better patient care a more cost-effective approach to the diagnosis of CD, and a greater awareness among health-care professionals.

Reprint requests and correspondence: Alessio Fasano, M.D., Mucosal Biology Research Center, University of Maryland School of Medicine, 20 Penn Street, Room 345, Baltimore, MD 21201.

Received April 18, 2006; accepted August 31, 2006.

REFERENCES

1. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: An evolving spectrum. *Gastroenterology* 2001;120:636–51.
2. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: A large multicenter study. *Arch Intern Med* 2003;163:286–92.
3. Catassi C, Fabiani E, Ratsch I-M, et al. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatr Suppl* 1996;412:29–35.
4. Zintzaras E, Germanis AE. Performance of antibodies against tissue transglutaminase for the diagnosis of celiac disease: Meta-analysis. *Clin Vaccine Immunol* 2006; 13:187–92.
5. Viljamaa M, Collin P, Huhtala H, et al. Is celiac disease screening in risk groups justified? A fourteen-year follow-up with special focus on compliance and quality of life. *Aliment Pharmacol Ther* 2005;22:317–24.
6. Fasano A. European and North American populations should be screened for coeliac disease. *Gut* 2003;52:168–9.
7. Murray JA, Van Dike C, Plevak MF, et al. Trends in the identification and clinical features of celiac disease in a North American community, 1950–2001. *Clin Gastroenterol Hepatol* 2003;1:19–27.
8. Harewood GC, Holub JL, Lieberman DA. Variation in small bowel biopsy performance among diverse endoscopy settings: Results from a national endoscopic database. *Am J Gastroenterol* 2004;99:1790–4.
9. Lagerquist C, Ivarsson A, Juto P, et al. Screening for adult coeliac disease—which serological marker(s) to use? *J Intern Med* 2001;250:241–8.
10. Oberhuber G, Granditsch G, Vogelsang H. The histopathology of coeliac disease: Time for a standardized report scheme for pathologists. *Eur J Gastroenterol Hepatol* 1999;11:1185–94.
11. Fernandez E, Blanco C, Garcia S, et al. Use of low concentrations of human IgA anti-tissue transglutaminase to rule out selective IgA deficiency in patients with suspected celiac disease. *Clin Chem* 2005;51:1014–6.
12. Mahmud FH, Murray JA, Kudva VC, et al. Celiac disease in type 1 diabetes mellitus in a North American community: Prevalence, serologic screening, and clinical features. *Mayo Clin Proc* 2005;80:1429–34.
13. Book L, Hart A, Black J, et al. Prevalence and clinical characteristics of celiac disease in Down's syndrome in a US study. *Am J Med Genet* 2001;98:70–4.
14. Lanzini A, Villanacci V, Apillan N, et al. Epidemiological, clinical and histopathologic characteristics of celiac disease: Results of a case-finding population-based program in an Italian community. *Scand J Gastroenterol* 2005;40: 950–7.
15. Gadewar S, Fasano A. Celiac disease: Is the atypical really typical? Summary of the recent National Institutes of Health Consensus Conference and latest advances. *Curr Gastroenterol Rep* 2005;7:455–61.
16. Cranney A, Rostom A, Sy R, et al. Consequences of testing for celiac disease. *Gastroenterology* 2005;128:S109–20.

17. Collin P. Should adults be screened for celiac disease? What are the benefits and harms of screening? *Gastroenterology* 2005;128:S104–8.
18. Verkasalo MA, Raitakari OT, Viikari J, et al. Undiagnosed silent celiac disease: A risk for underachievement? *Scand J Gastroenterol* 2005;40:1407–12.
19. Mustalahti K, Collin P, Sievanen H, et al. Osteopenia in patients with clinically silent coeliac disease warrants screening. *Lancet* 1999;354:744–5.
20. Mäki M, Mustalahti K, Kokkonen J, et al. Prevalence of celiac disease among children in Finland. *N Engl J Med* 2003;348:2517–24.
21. Metzger MH, Heier M, Mäki M, et al. Mortality excess in individuals with elevated IgA anti-transglutaminase antibodies: The KORA/MONICA Augsburg Cohort Study 1989–1998. *Eur J Epidemiol* 2006;21:359–65.
22. West J, Logan RFA, Hill PG, et al. Seroprevalence, correlates, and characteristics of undetected celiac disease in England. *Gut* 2003;52:960–5.
23. Dickey W, McMillan SA, Hughes DF. Identification of celiac disease in primary care. *Scand J Gastroenterol* 1998;33:491–3.
24. Sanders DS, Patel D, Stephenson TJ, et al. A primary care cross-sectional study of undiagnosed adult celiac disease. *Eur J Gastroenterol Hepatol* 2003;15:407–13.
25. Kapur N, Hunt I, Lunt M, et al. Primary care consultation predictors in men and women: A cohort study. *Br J Gen Pract* 2005;55:108–13.
26. Hin H, Bird G, Fisher P, et al. Coeliac disease in primary care: Case finding study. *BMJ* 1999;318:164–7.
27. Hill I, Fasano A, Schwartz R, et al. The prevalence of celiac disease in at-risk groups of children in the United States. *J Pediatr* 2000;136:86–90.
28. Lo W, Sano K, Lebowitz BA, et al. Changing presentation of adult celiac disease. *Dig Dis Sci* 2003;48:395–8.
29. Zipser RD, Farid M, Baisch D, et al. Physician awareness of celiac disease. A need for further education. *J Gen Intern Med* 2005;20:644–6.
30. Sategna-Guidetti C, Volta U, Ciacci C, et al. Prevalence of thyroid disorders in untreated adult celiac disease patients and effect of gluten withdrawal: An Italian multicenter study. *Am J Gastroenterol* 2001;96:751–7.
31. Hakanen M, Luotola K, Salmi J, et al. Clinical and subclinical autoimmune thyroid disease in adult celiac disease. *Dig Dis Sci* 2001;46:2631–5.
32. Valentino R, Savastano S, Tommaselli AP, et al. Prevalence of coeliac disease in patients with thyroid autoimmunity. *Horm Res* 1999;51:124–7.
33. Sollid LM, Lie BA. Celiac disease genetics: Current concepts and practical applications. *Clin Gastroenterol Hepatol* 2005;3:843–51.
34. Cash BD, Schoenfeld P, Chey WD. The utility of diagnostic tests in irritable bowel syndrome patients: A systematic review. *Am J Gastroenterol* 2002;97:2812–9.
35. Spiegel HM, DeRosa VP, Gralnek IM, et al. Testing for celiac sprue in irritable bowel syndrome with predominant diarrhea: A cost-effectiveness analysis. *Gastroenterology* 2004;126:1721–32.
36. Mein SM, Ladabaum U. Serological testing for celiac disease in patients with symptoms of irritable bowel syndrome: A cost-effectiveness analysis. *Aliment Pharmacol Ther* 2004;19:1199–210.
37. Unsworth DJ, Lock RJ, Harvey RF. Improving the diagnosis of celiac disease in anaemic women. *Br J Haematol* 2000;111:898–901.
38. Grisolano SW, Oxentenko AS, Murray JA, et al. The usefulness of routine small bowel biopsies in evaluation of iron deficiency anemia. *J Clin Gastroenterol* 2004;38:756–60.
39. Cataldo F, Marino V, Ventura A, et al. Prevalence and clinical features of selective immunoglobulin A deficiency in coeliac disease: An Italian multicentre study. Italian Society of Paediatric Gastroenterology and Hepatology (SIGEP) and “Club del Tenue” Working Groups on Coeliac Disease. *Gut* 1998;42:362–5.

CONFLICT OF INTEREST

Guarantor of the article: Alessio Fasano, M.D.

Specific author contribution: Carlo Catassi (study conception and design, data analysis and interpretation, drafting of article), Deborah Kryszak (data analysis and interpretation), Otto Louis-Jacques (study conception and design, critical revision, patient recruitment), Donald R. Duerksen, Ivor Hill, Sheila E. Crowe, Andrew R. Brown, Nicholas J. Procaccini, Brigid A Wonderly, Paul Hartley, James Moreci, Nathan Bennett (study design, patient recruitment and critical revision), Karoly Horvath (study design, critical revision), Margaret Burk (study design, data analysis, critical revision), Alessio Fasano (study conception and design, data analysis and interpretation, drafting of article and final approval).

Financial support: The study was partially supported by the Center for Celiac Research and the National Institutes of Health Grant DK-48373.

Potential competing interests: Alessio Fasano has financial interest in Alba Therapeutics, a company interested in developing alternative treatments for autoimmune diseases, including celiac disease.
