Prevalence of Celiac Disease Among First-degree Relatives of Patients With Celiac Disease

*Yaşar Doğan, †Serap Yıldırmaz, and ‡İbrahim Hanifi Özercan

ABSTRACT

Objectives: Celiac disease, an autoimmune enteropathy that affects the proximal small intestine, is characteristically seen in people who have a genetic susceptibility to gluten sensitivity. Celiac patients' first-degree relatives are more at risk of acquiring the disease. The objective of the present study was consequently to determine the prevalence of celiac disease in a group of first-degree relatives of our patients with celiac disease.

Methods: First-degree relatives of 195 patients with celiac disease attending a gastroenterology unit underwent serologic screening. Antitissue transglutaminase (anti-tTG) immunoglobulin A (IgA) and total serum IgA tests were used for first-level screening. Duodenal biopsy was recommended to subjects showing positive results to anti-tTG IgA testing. Biopsy samples were obtained by endoscopy, and biopsy specimens were evaluated and classified according to Marsh classification.

Results: Positive anti-tTG IgA was found in 46 first-degree relatives (9.5%), whereas serum IgA levels were normal. Of 46 serology-positive relatives, 34 agreed to the endoscopy procedure. Histological changes characteristic of celiac disease were found in 23 subjects. The prevalence of celiac disease among the first-degree relatives was found to be at least 4.8%. Of 34 subjects that underwent biopsy, 11 were evaluated as Marsh 0, 5 as Marsh 1, 4 as Marsh 2, 12 as Marsh 3, and 2 as Marsh 4. Of the biopsy-positive subjects, 3 were mothers, 1 was a father, and 19 were siblings.

Conclusions: The present study identified 23 undiagnosed cases of celiac disease among 484 first-degree relatives of 195 patients with celiac disease, confirming the high prevalence (4.8%) of the disease in this specific group. It is suggested that an extensive screening policy be mandatory for these subjects.

Key Words: celiac disease, first-degree relatives, prevalence, tissue transglutaminase immunoglobulin A

(*JPGN* 2012;55: 205–208)

Celiac disease (CD) is an autoimmune enteropathy characterised by persistent sensitivity to gluten that occurs following the intake of gluten-containing foods and affects the proximal small intestine of genetically predisposed people (1,2). Based on the clinical diagnosis, the incidence of CD ranges from 1:100 to 1:1000 (2–4). These data indicate the surprisingly high incidence of CD, which has historically been thought to be a rare disease in both at-risk groups and the overall population (5,6). Population screenings have revealed that asymptomatic cases are numerically greater than symptomatic cases (7–9). Especially amongst first-degree relatives of patients with CD, people with genetic disorders (eg, iron deficiency/anaemia, osteopenic bone disease, type 1 diabetes mellitus, hepatic disease, Down and Turner syndrome, autoimmune endocrinopathies, dermatitis herpetiformis, ataxia, neurological disorders such as seizures, immunoglobulin A [IgA] deficiency) show an increased risk for CD occurrence (10). The present study aimed to investigate the prevalence of CD in our region by performing screening tests on the first-degree relatives of our patients diagnosed with CD.

METHODS

The present study included first-degree relatives of 224 subjects being studied with a diagnosis of CD in the Paediatric Gastroenterology Department. Parents and siblings of these subjects were invited to our clinic via letter or telephone to participate in the study. Twenty-nine patients who did not come to our clinic and those who came to our clinic but refused to participate in the study were excluded, as were their first-degree relatives. First-degree relatives of the remaining 195 patients were included in the study (113 mothers, 109 fathers, and 262 siblings). Before starting, the study was approved by the ethics board of Fırat University, and all of the families enrolled in the study provided written informed consent. The study was conducted in 2 phases.

In the first phase, all of the subjects provided serum samples. A 3-mL venous blood sample was drawn into a gel tube, left to coagulate, and centrifuged at 3000 rpm for 3 minutes. Thereafter, the serum sample, which was separated, was stored in a gel-free tube until the time of analysis at a temperature of -80°C. On the day of study, serum samples were thawed and used immediately. Separated serum samples were analysed for antitissue transglutaminase (anti-tTG) IgA and serum IgA. Anti-tTG IgA was analysed via the enzyme-linked immunosorbent assay method using Seramun Diagnostica GmbH's Serazym anti-tTG IgA kits (Heidesee, Germany). Anti-tTG IgA antibody levels $\geq$20 U/mL were considered positive. Serum IgA was analysed via the nephelometric method using Dade Behring Marburg GmbH's N antiserum human immunoglobulin kits (Marburg, Germany). The subjects with IgA values less than normal for their age groups were considered IgA deficient because the age groups of the subjects differed.

In the second phase, in the subjects who had been found to be positive for the anti-tTG IgA antibody, sedoanalgesia was provided using intravenous 0.1 to 0.4 mg/kg (max 10 mg/dose) midazolam and $1\,\mathrm{mg}\cdot\mathrm{kg}^{-1}\cdot\mathrm{dose}^{-1}$ (max 75 mg) pethidine hydrochloride, and local pharynx anaesthesia was provided using xylocaine 10% spray. Following this, patients fasted for at least 6 hours, and upper gastrointestinal system endoscopy was performed using a paediatric endoscopy device (Olympus Evis Lucera CLV-260SL paediatric videoendoscope, Olympus, Tokyo, Japan). During the

Received August 9, 2011; accepted December 29, 2011.

From the *Department of Pediatrics, Division of Pediatric Gastroenterology Hepatology and Nutrition, the †Departments of Pediatrics, and the ‡Department of Pathology, Fırat Medical Faculty, Fırat University, Elazığ, Turkey.

Address correspondence and reprint requests to Yaşar Doğan, MD, Fırat Üniversitesi Hastanesi Çocuk Sağ. ve Hast, Anabilim Dalı, 23119 Elazığ, Turkey (e-mail: yasardogan@ttmail.com).

The authors report no conflicts of interest.

Copyright © 2012 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

DOI: 10.1097/MPG.0b013e318249378c

Copyright 2012 by ESPGHAN and NASPGHAN. Unauthorized reproduction of this article is prohibited.

TABLE 1. Anti-tTG IgA and biopsy results of the subjects

	Subjects		Anti-tTG IgA positive		Subjects who underwent biopsy		Patients with celiac disease	
	n	%	n	%	n	%	n	%
Mother	113	23.4	5	10.9	5	14.7	3	13.0
Father	109	22.5	5	10.9	3	8.8	1	4.4
Sibling	262	54.1	36	78.2	26	76.5	19	82.6
Total	484	100	46	100	34	100	23	100

Anti-tTG = antitissue transglutaminase; IgA = immunoglobulin A.

endoscopy, 3 samples of small intestine biopsy were obtained from the second part or more distal parts of the duodenum using biopsy forceps. Biopsy samples obtained were put in formaldehyde and sent to Fırat University, Faculty of Medicine, Department of Pathology. All of the pathological examinations of the biopsy samples obtained were performed by the same pathologist. Biopsy samples were evaluated using haematoxylin and eosin staining. For intraepithelial lymphocyte counting, immunohistochemistry (leukocyte common antigen) was used. Intraepithelial lymphocytosis was defined as the presence of >30 intraepithelial lymphocytes for each 100 epithelial cells using leukocyte common antigen staining. Mucosal alterations were defined using Marsh scoring (11).

For statistical analyses, SPSS 12.0 software (SPSS Inc, Chicago, IL) was used. Differences in anti-tTG IgA levels (in terms of sex, degree of relationship [ie, mother, father, or sibling], and whether the categorical variable of anti-tTG IgA positivity/negativity status was significantly different in terms of relationship and sex) were analysed using the χ^2 test. Values of $P < 0.05$ were considered significant.

RESULTS

Of the 484 subjects enrolled in the study, 113 (23.3%) were mothers, 109 (22.5%) were fathers, and 262 (54.1%) were siblings. Of the siblings, 149 (56.9%) were sisters and 113 (43.1%) were brothers. Of the subjects, 46 (9.5%) were anti-tTG IgA-positive. None of the subjects showed IgA deficiency. Because 12 of anti-tTG IgA-positive subjects did not agree to undergo an endoscopic biopsy procedure, only 34 subjects underwent biopsy. In 23 of the 34 subjects (67.6%), the result obtained from the biopsy was considered consistent with CD. Therefore, at least 4.8% of the subjects enrolled in the study had the diagnosis of CD because 12 subjects who were seropositive refused biopsy. If we had been able to perform biopsies on these 12 subjects, the prevalence percentage rate would have increased further. Of the 34 subjects who underwent the biopsy procedure, 11 were evaluated as Marsh 0, 5 as Marsh 1, 4 as Marsh 2, 12 as Marsh 3, and 2 as Marsh 4. We considered the 11 subjects with Marsh 0 as those with potential CD because the tTG IgA levels of these subjects were high, and they had no obvious GI complaints. Of the 23 subjects who were considered as having CD, 3 were mothers, 1 was a father, and 19 were siblings (Table 1). Among these subjects considered as having CD, the 3 mothers and the father had no obvious complaints. Ten of the 19 siblings had no complaints, whereas 6 of them were shorter than their peers. The remaining 3 subjects had dyspeptic complaints and abdominal pain, which were not considered important. The laboratory values of the new cases of CD, such as haemoglobin, haematocrit, ferritin, or aminotransferases, were not known at the beginning of the study during the initial diagnosis.

Although the study included more female subjects than male subjects, no statistically significant difference was found between anti-tTG IgA positivity or negativity ($P = 0.082$) (Table 2). It was found that the prevalence of anti-tTG IgA positivity was statistically higher in siblings than in mothers and fathers ($P = 0.003$) (Table 3).

DISCUSSION

With the introduction of serological tests and screening studies, it was revealed that the incidence of CD has been underestimated (10). CD is a condition that is well known to be caused by a genetic predisposition, and therefore its prevalence in the first-degree relatives of patients with CD is higher than that of the non-CD population. If, in a given family, ≥2 siblings are affected, the risk is increased further (12–14). Given that the prevalence of CD in the general population is high, with a rate of 1% (8), in the presence of >1 patient with CD in the family, the prevalence of CD in first-degree relatives ranges between 17.2% and 21.3% (12).

TABLE 2. Results of χ^2 test for anti-tTG IgA negativity/positivity according to sex of the subjects enrolled in the study and female/male ratio

	Anti-tTG IgA, U/mL		
No. subjects	0–20 n (%)	>20 n (%)	Total n (%)
Female	231 (88.2)	31 (11.8)	262 (100)
Male	207 (93.2)	15 (6.8)	222 (100)
Total	438 (90.5)	46 (9.5)	484 (100)
Female/male ratio	1.11	2.06	1.18

$\chi^2 = 3.033$, $P = 0.082$. Anti-tTG = antitissue transglutaminase; IgA = immunoglobulin A.

Copyright 2012 by ESPGHAN and NASPGHAN. Unauthorized reproduction of this article is prohibited.

TABLE 3. Results of χ^2 test for anti-tTG IgA negativity/positivity according to relationship of the subject enrolled in the study to the patient with celiac disease

	tTG negative		tTG positive		
Relationship	n	%	n	%	Total
Mother	108	95.6	5	4.4	113
Father	104	95.4	5	4.6	109
Sibling	226	86.3	36	13.7	262
Total	438		46		484

$\chi^2 = 11.92$, $P = 0.003$. Anti-tTG = antitissue transglutaminase; IgA = immunoglobulin A.

Therefore, various studies were conducted to investigate its prevalence in the first-degree relatives of patients with CD and to create an algorithm. First-degree relatives of patients with CD represent an ideal target group for serological screening because the prevalence of positive findings is higher in this group compared with the general population and other at-risk groups. In the screening studies based on serological tests conducted on first-degree relatives of patients with CD, different results were reported concerning the prevalence of the disease. These differences may be partly explained by methodological differences and the differences of genetic origin observed in the communities evaluated across the studies (13).

In a Spanish study performed by Farre et al (15), 675 first-degree relatives of 227 patients with CD were examined for endomysium antibody (EMA), anti-gliadin antibody (AGA) IgA, human leukocyte antigen-DQ2 haplotype, and the clinical findings of CD. EMA was positive in 5.8% and AGA IgA was positive in 1.9% of the subjects. The rate of biopsy-confirmed CD assessed as 5.5% was found to be higher in the siblings compared with the mothers and fathers (respectively, 12% and 3%). In one-third of the relatives, clinical findings of CD (eg, diarrhoea, anaemia, food intolerance, growth retardation) were not present. Therefore, in first-degree relatives, screening was recommended, regardless of clinical complaint. In a study conducted in the United States, the prevalence of CD was investigated in families in which 2 siblings had CD. Serology (EMA and anti-tTG IgA) and/or biopsy positivity defined the presence of CD. Although it was found that the risk was markedly increased with the prevalence of 17.2% in 163 first-degree relatives enrolled in the study and 21.3% in the siblings, no difference was found in terms of sex (12). In our study, although there were more female subjects than male subjects, no statistically significant difference was found.

In Italy, 441 first-degree relatives of 208 patients with CD were enrolled in a study. EMA and anti-tTG IgA were examined. Although anti-tTG IgA was positive in 46 subjects, EMA was positive in 38 subjects. Forty subjects had the diagnosis of CD confirmed by biopsy, and the prevalence of CD was 9.5% (16).

In our study, anti-tTG IgA positivity was observed in 46 of 484 subjects (9.5%). A total of 23 first-degree relatives (4.8%, including 3 mothers, 1 father, and 19 siblings) had biopsy-confirmed CD diagnoses. When compared with the prevalence found in the studies conducted with healthy children in Turkey, these rates were 7.5-fold higher than those reported by Ertekin et al (17) and 9.5-fold higher than those reported by Dalgıc et al (18), supporting the notion that this group showed a higher risk than the non-CD population. The prevalence of biopsy-confirmed CD in first-degree relatives varied from 2.8% to 12% across the studies performed (13–16,19–21). In our study, the prevalence rate was consistent with the literature (4.8%). In first-degree relatives, serology-confirmed CD prevalence varied between 5.8% and 14% (14–16,20), and our prevalence rate of 9.5% was found to be consistent with the literature. In some studies, it was reported that the siblings and parents were equally affected (13,22,23). Based on the results of our study, consistent with the results of Book et al (12) and Farre et al (15), we observed that the siblings (7.2%) were more affected than the parents (1.8%).

In the study performed by Almeida et al (13) on 188 first-degree relatives, 9 (4.8%) subjects had confirmed CD. Of these subjects, 8 had a Marsh score of 3 and 1 had a Marsh score of 1. Of the subjects in our study diagnosed as having CD, 5 had a Marsh score of 1, 4 had a Marsh score of 2, 12 had a Marsh score of 3, and 2 had a Marsh score of 4. Eleven (2.27%) subjects with anti-tTG IgA positivity were considered patients with CD despite normal biopsy of the small intestine and were monitored.

Consequently, in the first-degree relatives included in the present study, the percentage of anti-tTG IgA positivity was 9.5%, and the percentage of confirmed CD was 4.8%, supporting the insight that the development of an extensive screening approach is necessary to promote early diagnosis and prevent the complications of untreated disease in first-degree relatives of patients with CD.

REFERENCES

1. Ciclitira PJ, King AL, Fraser JS. AGA technical review on celiac sprue. *Gastroenterology* 2001;120:1526–40.
2. Garcia-Careaga M. Gluten-sensitive enteropathy (celiac disease, celiac sprue). In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics.* 17th ed. Philadelphia: Saunders; 2004: 1264–6.
3. Trier JS. Diagnosis of celiac sprue. *Gastroenterology* 1998;115: 211–6.
4. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001;120: 636–51.
5. Talley NJ, Valdovinos M, Petterson TM, et al. Epidemiology of celiac sprue: a community-based study. *Am J Gastroenterol* 1994; 89:843–6.
6. Not T, Horvath K, Hill ID, et al. Celiac disease risk in the USA: high prevalence of antiendomysium antibodies in healthy blood donors. *Scand J Gastroenterol* 1998;33:494–8.
7. Fasano A. Clinical presentation of celiac disease in the paediatric population. *Gastroenterology* 2005;128:68–73.
8. Hill ID. Celiac disease—a never-ending story? *J Pediatr* 2003;143: 289–91.
9. Book LS. Diagnosing celiac disease in 2002: who, why, and how? *Pediatrics* 2002;109:952–4.
10. Freeman HJ. Risk factors in familial forms of celiac disease. *World J Gastroenterol* 2010;16:1828–31.
11. Marsh MN. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology* 1992;102:330–54.

Copyright 2012 by ESPGHAN and NASPGHAN. Unauthorized reproduction of this article is prohibited.

12. Book L, Zone JJ, Neuhausen SL. Prevalence of celiac disease among relatives of sib pairs with celiac disease in U.S. families. *Am J Gastroenterol* 2003;98:377–81.
13. Almeida PL, Gandolfi L, Modelli IC, et al. Prevalence of celiac disease among first-degree relatives of Brazilian celiac patients. *Arq Gastroenterol* 2008;45:69–72.
14. Esteve M, Rosinach M, Fernandez-Banares F, et al. Spectrum of gluten-sensitive enteropathy in first-degree relatives of patients with coeliac disease: clinical relevance of lymphocytic enteritis. *Gut* 2006; 55: 1739–45.
15. Farre C, Humbert P, Vilar P, et al. Serological markers and HLA-DQ2 haplotype among first-degree relatives of celiac patients. *Dig Dis Sci* 1999;44:2344–9.
16. Bonamico M, Ferri M, Mariani P, et al. Serologic and genetic markers of celiac disease: a sequential study in the screening of first-degree relatives. *J Pediatr Gastroenterol Nutr* 2006;42:150–4.
17. Ertekin V, Selimoglu MA, Kardas F, et al. Prevalence of celiac disease in Turkish children. *J Clin Gastroenterol* 2005;39:689–91.
18. Dalgıc B. Prevalance of celiac disease in Turkish school children. Paper presented at: 43rd annual meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. İstanbul: abstract booklet; 2010:152.
19. 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.
20. Rubio-Tapia A, Van Dyke CT, Lahr BD, et al. Predictors of family risk for celiac disease: a population-based study. *Clin Gastroenterol Hepatol* 2008;6:983–7.
21. Dolinsek J, Urlep D, Karell K, et al. The prevalence of celiac disease among family members of celiac disease patients. *Wien Klin Wochenschr* 2004;116:8–12.
22. Fraser JS, King AL, Ellis HJ, et al. An algorithm for family screening for coeliac disease. *World J Gastroenterol* 2006;12:7805–9.
23. Srivastava A, Yachha SK, Mathias A, et al. Prevalence, human leukocyte antigen typing and strategy for screening among Asian first-degree relatives of children with celiac disease. *J Gastroenterol Hepatol* 2010;25:319–24.

Copyright 2012 by ESPGHAN and NASPGHAN. Unauthorized reproduction of this article is prohibited.