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ORIGINAL ARTICLE—ALIMENTARY TRACT

Celiac disease in non-clinical populations of Japan

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Abstract
Background Celiac disease is a chronic autoimmune enteropathy caused by gluten ingestion. While its prevalence in Western countries is reported to be as high as 1%, the prevalence has not been evaluated in a large-scale study of a Japanese population. The aim of our study was to clarify the possible presence of celiac disease in a Japanese non-clinical population as well as in patients showing symptoms suggestive of the disease.
Methods Serum samples were collected from 2008 non-clinical adults and 47 patients with chronic unexplained abdominal symptoms between April 2014 and June 2016. The anti-tissue transglutaminase (TTG) immunoglobulin A antibody titer was determined as a screening test for celiac disease in all subjects, and individuals with a value of >2 U/mL subsequently underwent testing for the presence of serum endomysial IgA antibody (EMA) as confirmation. Those testing positive for EMA or with a high concentration (>10 U/mL) of TTG were further investigated by histopathological examinations of duodenal mucosal biopsy specimens and HLA typing tests.
Results Of the 2008 non-clinical adults from whom serum samples were collected, 161 tested positive for TTG, and all tested negative for EMA. Four subjects who had a high TTG titer were invited to undergo confirmatory testing, and the histopathological results confirmed the presence of celiac disease in only a single case (0.05%). Of the 47 symptomatic patients, one (2.1%) was found to have a high TTG titer and was diagnosed with celiac disease based on duodenal histopathological findings.
Conclusion The presence of celiac disease in a non-clinical Japanese population was low at 0.05% and was rarely found in patients with unexplained chronic abdominal symptoms.

Keywords Celiac disease · Anti-tissue transglutaminase IgA · Antibody · HLA

Introduction

Celiac disease is an immune-mediated disorder induced by ingestion of gluten in genetically susceptible individuals [1, 2]. Immune-mediated chronic inflammation mainly occurs in the proximal intestine where it induces intramucosal lymphocyte infiltration and villous atrophy. The classic symptoms of patients with the disease are nutritional malabsorption and chronic diarrhea. However, it has become clear that the majority of celiac disease patients do not have classic symptoms, but rather non-specific abdominal and extra-abdominal symptoms and signs [3–6], while asymptomatic cases have also been reported. Therefore, diagnostic tests are recommended even for asymptomatic cases when the patient is considered to be at risk [7].

Diagnosis of celiac disease is mainly based on two types of examinations, screening and confirmatory tests [1, 2, 8, 9]. First, the presence and amount of serum antibodies against gluten and its related molecules are

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determined in a screening test, with the most widely used and sensitive tests currently available being the measurement of antibodies against tissue transglutaminase (TTG) and endomysium [9, 10]. When a patient shows a positive result in these serological tests, endoscopic observation and histopathological examination of duodenal mucosal biopsy specimens is a confirmatory test that must be performed [1, 2, 11]. Typing of the human leukocyte antigen (HLA) complex is another important test used to detect susceptible individuals, at least in Western populations [12].

The prevalence of celiac disease in Caucasians is reported to be increasing and has been reported to be as high as 1% of the population [7, 13–15]; it is therefore considered to be a rather common condition in Western countries. To the contrary, the disease is considered to be very rare in Japan, partly because of the limited consumption of a gluten-containing diet as well as the lower prevalence of the celiac disease-susceptible HLA types HLA-DQ2 and -DQ8 [16–19]. However, the consumption of gluten, mainly in wheat products, is steadily increasing in Japan [20, 21], possibly leading to an increase in the prevalence of celiac disease, not only as cases of unexplained abdominal symptoms, but also in asymptomatic non-clinical individuals.

The aim of the study reported here was to investigate the possible presence of celiac disease in Japanese patients with abdominal symptoms without proven organic gastrointestinal disease as well as in local residents of Japan.

Methods

Subjects

Individuals who visited the Health Center of Shimane Environmental and Health Public Corporation were enrolled as the non-clinical group. These participants did not have symptoms that led them to visit a clinic or hospital. Patients who visited the outpatient clinic of Shimane University Hospital with chronic abdominal symptoms, including dyspepsia and diarrhea, were also enrolled. Only those patients without structural disease that may have caused their symptoms were consecutively enrolled. Study enrollment began in April 2014 and ended in June 2016.

Screening test

Serum was collected from each of the participants in a fasted state and stored at −30 °C until assayed. For those in the non-clinical group, serum samples remaining after testing as part of the routine medical health check were used. Serum samples were assayed for the presence of anti-TTG antibody with an ORG 540A Anti-Tissue-Transglutaminase IgA ELISA kit (ORGENTEC Diagnostika GmbH, Mainz, Germany), performed according to the instructions of the manufacturer. This test quantitatively measures the concentration of the anti-human TTG immunoglobulin A (IgA) antibody [10]. The cutoff value is 2 U/mL, and individuals identified with a higher concentration are subsequently tested for the presence of serum IgA EMA antibody as conformation (Quest Diagnostic Inc., Chantilly, VA). In the anti-endomysial antibody (EMA) test, antibodies from the patient's serum bind to connective tissue surrounding smooth muscle cells of monkey esophagus and are detected by immunofluorescence.

Confirmatory tests

Participants who tested positive for EMA were invited to undergo confirmatory examinations. All patients presenting TTG-positive results with TTG levels of >10 U/mL were also invited, regardless of EMA results, to undergo further testing. All participants issued such an invitation agreed to further testing. After a complete medical history had been taken and physical examinations performed, blood samples were obtained for complete blood cell counts and serum biochemical analyses. HLA typing was also performed to detect the susceptible loci HLA-DQ2 and -DQ8 [22].

The duodenal mucosal surface down to the second duodenal portion was thoroughly checked in an upper gastrointestinal (GI) endoscopic examination as part of the confirmatory examinations [7, 23], during which at least four biopsy specimens from the duodenal mucosa were obtained for histopathological examinations according to previously presented guidelines [1]. The length and density of villi, depth of crypts, and density of intraepithelial lymphocyte infiltration were determined in the pathological specimens according to the modified Marsh classification [24, 25]. Immunohistochemistry studies on CD3 (clone 2GV6; Roche Diagnostics K.K., Yokohama, Japan) were carried out in all participants to better identify and quantify intraepithelial lymphocytes. Histopathological findings were separately and independently reviewed by three pathologists (NI, AA, RM), who had no information regarding the TTG and EMA results. When the diagnosis of the classification differed among the pathologists, they viewed the pathological specimens together and arrived at a final diagnosis based on consensus after discussion.

The protocol of the study was approved by the Ethical Committee of Shimane University School of Medicine and written informed consent was obtained from all participants. This study was registered with the University Hospital Medical Information Network (UMIN) clinical trials registry (UMIN 000013578).

Results

Non-clinical subjects

A total of 2008 local residents, ranging in age from 25 to 80 years, who attended an annual health check-up were enrolled in the study (Table 1). All participants initially underwent a TTG test, which resulted in the identification of 161 (8.0%) individuals who tested positive for TTG at a concentration of >2 U/mL and four (0.2%) who tested positive for TTG at a concentration of >10 U/mL. These individuals then underwent testing for EMA, which revealed that none of these individuals were positive for EMA.

The four non-clincial subjects who were found to have a high TTG titer (>10 U/mL) were invited to undergo confirmatory testing, and all accepted (Table 2). All four individuals were male and in their 50s and 60s. HLA typing detected only one subject with a susceptible immunotype (DQ8); the remaining three subjects possessed other non-susceptible HLA types. Although endoscopic observation of the duodenal mucosa did not detect any abnormalities in any of these four subjects, histological examinations of duodenal mucosal biopsy specimens revealed subtotal atrophy of the villi with moderate inflammatory cell infiltration in a single subject (Case 2), who did not have a susceptible HLA type (Fig. 1). Immunohistochemical staining with a monoclonal antibody to human CD3 showed increased intraepithelial lymphocytes with villous atrophy. According to histological grading based on the modified Marsh classification, a biopsy specimen from the duodenal mucosa was diagnosed as grade 3B, which was compatible with histological changes observed in celiac disease. The score arrived at by the three pathologists matched completely.

This subject (Case 2) complained of frequent diarrhea at least four times a week, but did not have other symptoms. Physical examination findings were unremarkable, as were laboratory blood and urine test results. Thus, only one of the four subjects with a high TTG titer was ultimately diagnosed with celiac disease based on clinical symptoms and duodenal histopathological findings. Globally, of the 2008 local Japanese residents who underwent a voluntary health check, only one (0.05%) was found to have celiac disease.

Table 1 Demographic and clinical characteristics of enrolled non-clinical subjects

Patient characteristics	Values
Number of subjects	2008
Sex (male/female, *n*)	1351/657
Median age, years (range)	53 (25–80)
Age distribution, years (male/female, *n*)	
~39	82/51
40~49	382/222
50~59	611/295
60~69	241/78
70~	35/11
BMI (kg/m^2)[a]	23.0 ± 3.3
Current drinker, *n* (%)	1193 (59.4)
Symptoms, *n* (%)[b]	
Heartburn	73 (3.6)
Upper abdominal pain	100 (5.0)
Abdominal fullness	147 (7.3)
Anorexia	28 (1.4)
Constipation	205 (10.2)
Diarrhea	178 (8.9)
Comorbidity, *n* (%)[b]	
Cardiovascular disease	410 (20.4)
Pulmonary disease	77 (3.8)
Cerebrovascular disease	25 (1.2)
Gastrointestinal disease	120 (6.0)
Hepato-billiary disease	99 (4.9)
Hyperlipidemia	322 (16.0)
Diabetes	119 (5.9)
Anemia	50 (2.5)

BMI Body mass index

[a] BMI is given as the mean ± standard deviation (SD)

[b] Duplicates counted

Symptomatic patients

Forty-seven patients with unexplained abdominal symptoms, including diarrhea, abdominal pain, and bloating, were enrolled in the study (Table 3). Standard clinical, blood, and urine, laboratory tests, as well as imaging studies, including an endoscopic examination, did not detect diseases that may have caused these symptoms. A TTG test was also performed as a screening test, and two (4.3%) patients were subsequently asked to take the EMA test. Although both of these latter two patients tested negative for EMA, one patient (male, 72 years old), who reported long-lasting diarrhea, had a high TTG titer (29.8 U/mL). An endoscopic examination of the duodenal mucosa of this patient suggested possible atrophy, which was confirmed by histopathological findings.

The duodenal mucosa in a biopsy specimen of this patient showed total atrophy of the villi, with severe inflammatory cell infiltration and basal cells. The modified Marsh classification of the biopsy specimen was assessed

Table 2 Demographic and clinical characteristics of the four non-clinical subjects who tested positive for tissue transglutaminase

Patient characteristics	Case 1	Case 2	Case 3	Case 4
Age	58	66	56	52
Sex	Male	Male	Male	Male
TTG IgA titer (U/mL)	11.4	12.9	20.6	10.1
EMA test	Negative	Negative	Negative	Negative
Duodenal histology (Marsh classification)	0	3B	0	0
Symptoms	–	Diarrhea	–	–
BMI (kg/m^2)	21.1	20.3	23.5	21.9
Hemoglobin (g/dL)	14.1	15.0	14.8	14.4
Albumin (g/dL)	4.6	4.7	4.5	4.6
CRP (mg/dL)	0.04	0.04	0.01	0.01
HLA type	DQ-6, -8	DQ-4, -6	DQ-7, -9	DQ-6, -9

TTG Tissue transglutaminase, *EMA* endomysial antibody, *CRP* C-reactive protein, *HLA* human leukocyte antigen

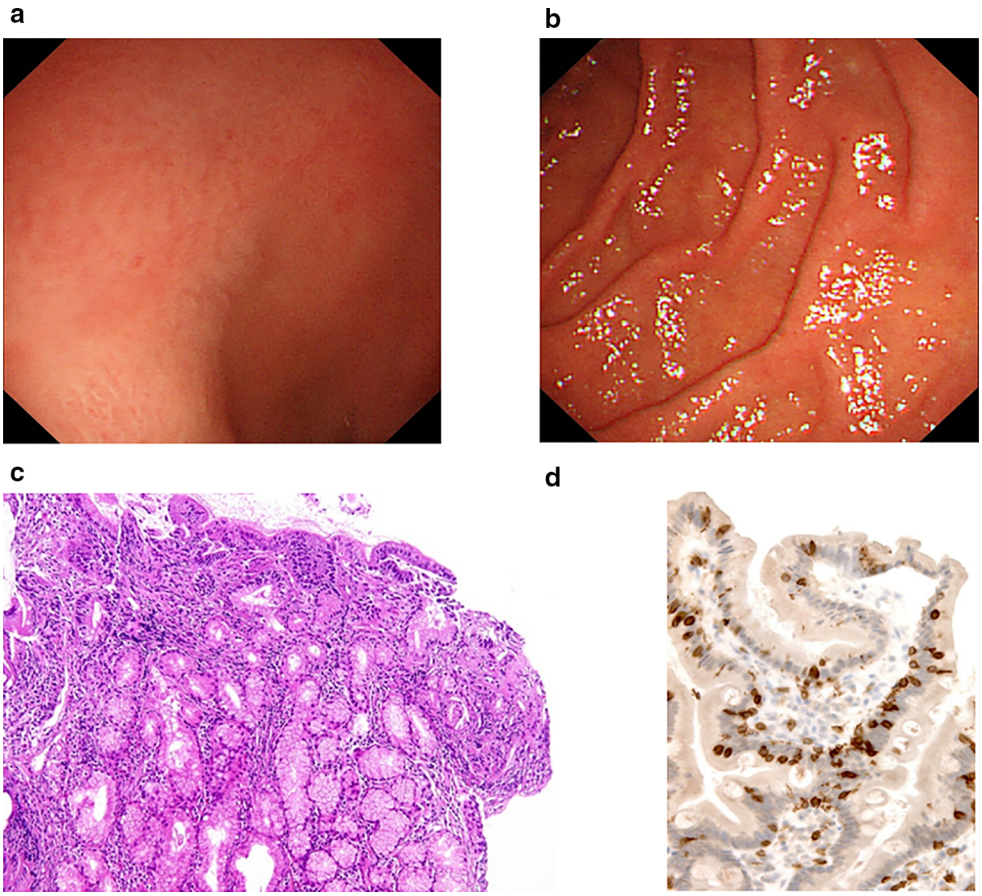

Fig. 1 Endoscopic and histological findings of duodenal mucosa in a non-clinical subject who tested positive for tissue transglutaminase (TTG) (Case 2). **a**, **b** Conventional endoscopic observation of duodenal mucosa did not reveal any abnormalities. **c** The duodenal mucosa showed subtotal atrophy of the villi with moderate inflammatory cell infiltration (hematoxylin-eosin staining, original magnification ×5). **d** Immunohistochemical staining with a human CD3 monoclonal antibody increased intraepithelial lymphocytes (original magnification ×20). The biopsy specimen was graded as 3B using the modified Marsh classification

as grade 3C by the three pathologists (Fig. 2). Therefore, the patient was diagnosed with celiac disease and treated with a gluten-free diet. No susceptible HLA type was detected, as the HLA types were found to be HLA-DQ6 and -DQ7. The diarrhea symptoms improved after the patient was started on the gluten-free diet.

Table 3 Demographic and clinical characteristics of patients enrolled in the study

Patient characteristics	Values
Number of patients	47
Sex (male/female, *n*)	21/26
Median age in years (range)	64 (17–84)
BMI (kg/m^2)[a]	21.3 ± 3.7
Current smoker, *n* (%)	4 (8.5)
Current drinker, *n* (%)	14 (29.8)
Symptoms, *n* (%)[b]	
Upper abdominal pain	13 (27.7)
Abdominal fullness	10 (21.3)
Diarrhea	28 (59.6)
Body weight loss	3 (6.4)
Comorbidity, *n* (%)[b]	
Cardiovascular disease	8 (17.0)
Pulmonary disease	2 (4.3)
Cerebrovascular disease	1 (2.1)
Gastrointestinal disease	8 (17.0)
Diabetes	2 (4.3)

[a] BMI is given as the mean ± SD

[b] Duplicates counted

Discussion

Celiac disease is an immune-mediated chronic gastrointestinal disease caused by immune reactions against gluten and its metabolites. Since gluten is mainly contained in wheat crops, celiac disease is more common in areas where dietary consumption of wheat products is high [13]. In addition, individuals possessing the HLA immunotypes HLA-DQ2 and -DQ8 are reported to be susceptible, and nearly all patients with celiac disease in Western countries have been reported to possess at least one of these HLA types [9, 22]. The incidence of celiac disease is high and increasing in Western countries due to the greater consumption of wheat products and the higher prevalence of HLA-DQ2 and -DQ8 (>25% of the general population), [13, 26, 27].

In Japan, the prevalence of the HLA-DQ2 and -DQ8 immunotypes has been reported to be very low, with an estimated HLA-DQ2 prevalence of 0.3%, based on tested samples obtained from a blood donor cohort [28]. In addition to this lower prevalence of susceptible HLA types, dietary consumption of wheat products in Japan is still one-third of that seen in Western countries, although consumption levels have been increasing in recent decades. Therefore, in clinical practice in Japan, celiac disease is rarely considered as a possible pathogenetic factor for unexplained abdominal symptoms, including diarrhea and malnutrition.

In Western countries, it is recommended that celiac disease should be considered as causative for patients with irritable bowel syndrome and other non-structural diseases manifesting various abdominal symptoms [29–31]. The TTG IgA ELISA is a sensitive and reliable screen test and is widely used to screen for celiac disease in patients with unexplained abdominal symptoms [2, 10, 32, 33]. Those patients who test positive for TTG (>2.0 U/mL) should then be asked to undergo testing for serum IgA EMA as confirmation. If the EMA test is positive, celiac disease can be diagnosed without duodenal biopsy [34].

Although this type of screening is considered to be effective in Western countries, where the prevalence of celiac disease is approximately 1% of the population, in countries where that prevalence is lower, the cost-effectiveness may not be adequate, and such testing is likely to be considered not useful.

The present study was conducted with a large cohort of local residents in Japan who underwent a medical check and showed a very low presence (0.05%) of celiac disease in comparison with populations in Western countries [13]. Based on these results, we suggest that the prevalence of celiac disease in Japan is extremely low as compared to that in Western countries, indicating a limited value for routine screening of Japanese populations. Our observation coincides with results from another study that found a very low prevalence of celiac disease in Japanese patients diagnosed with inflammatory bowel disease [19]. It is notable that the one non-clinical subject diagnosed with celiac disease based on clinicopathological findings possessed neither HLA-DQ2 nor -DQ8, which differs from observations in Western populations. In addition, a patient who visited our outpatient clinic for long-lasting diarrhea and subsequently diagnosed with celiac disease based on results of a duodenal mucosal histopathological examination and response to a gluten-free diet also lacked the HLA-DQ2 and -DQ8 immunotypes. Although HLA-DQ2 and -DQ8 are known to be appropriate for antigen presentation of gluten-derived peptides and 99% of patients with celiac disease in Western countries carry at least one of these types, other types of HLA may be responsible for the development of celiac disease in Japanese individuals, as the prevalence rates of HLA-DQ2 and -DQ8 are very low in Japan [2, 28, 35–38]. There have been only a few reports on the clinical characteristics of patients with celiac disease without HLA-DQ2 and -DQ8. A study conducted in Italy showed that among 437 patients with celiac disease, HLA-DQ2 and/or -DQ8 were more frequently present in the female patients than in the male patients although, in contrast, the majority of the 39 HLA-DQ2- and -DQ8-negative cases were male patients [39]. These results suggest that sex-specific differences in the HLA-DQ determined genetic susceptibility to celiac disease. Our patients with celiac disease were consistently male. Nonetheless, larger scale, nation-wide analysis is needed for the precise prevalence of celiac disease in Japan.

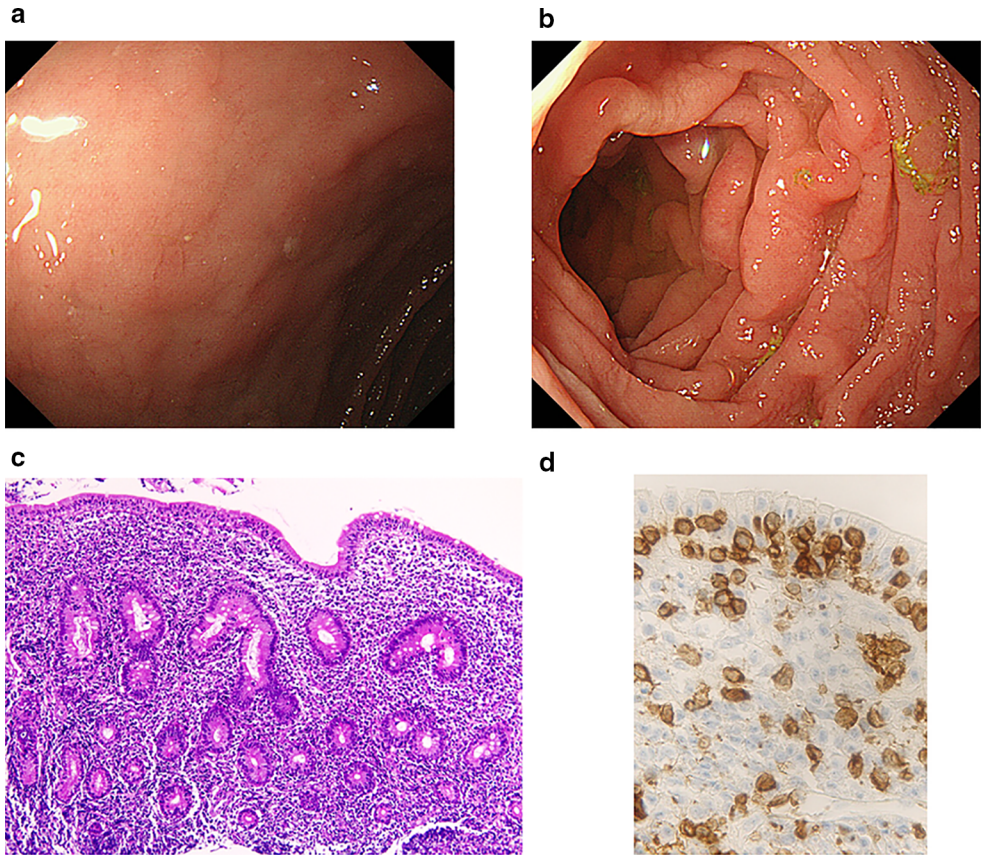

Fig. 2 Endoscopic and histological findings of specimen from duodenal mucosa in a symptomatic patient who tested positive for TTG. **a**, **b** Conventional endoscopic examination of the duodenal mucosa revealed edema and suggested possible atrophy. **c** The duodenal mucosa showed total atrophy of the villi with severe inflammatory cell infiltration and basal cell hyperplasia (hematoxylin-eosin staining, original magnification ×5). **d** Immunohistochemical staining with a human CD3 monoclonal antibody showed increased intraepithelial lymphocytes (original magnification ×20). The biopsy specimen was graded as 3C using the modified Marsh classification

The recent increased consumption of wheat products in Japan has been expected to increase the prevalence of celiac disease [20, 21]. However, our findings demonstrate a very low presence in local residents, suggesting a limited role of the disease as a pathogenetic cause of unexplained abdominal symptoms. Indeed, of the 47 patients with unexplained abdominal symptoms, we found only a single case of celiac disease that was confirmed by TTG test and clinicopathological findings. Therefore, the value of routine screening test for the disease can be considered to be limited in Japanese patients with unexplained chronic abdominal symptoms.

This study has several strong points. It is the first study to present the results of screening Japanese local residents for celiac disease. Also, the 2008 enrolled subjects is the largest cohort reported to date in such as screening study assessed by both TTG and EMA testing. Although there no participant tested positive for EMA, all five patients with a high TTG titer (10 U/mL) were further investigated by both histopathological and HLA typing examinations. On the other hand, the small number of symptomatic patients investigated in our study is a major limitation. A study that includes a greater number of symptomatic Japanese patients will be necessary in future.

In conclusion, the presence of celiac disease in a non-clinical Japanese population was low at 0.05%. Furthermore, in 47 Japanese patients with chronic unexplained abdominal symptoms, only a single case of the disease was found. Even with the increasing consumption of wheat products in Japan, the incidence of celiac disease seems to remain quite low as compared to Western countries.

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