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REVIEW

- 1187** Epidemiology of stomach cancer
Ilic M, Ilic I
- 1204** Antibiotics, gut microbiota, and irritable bowel syndrome: What are the relations?
Mamieva Z, Poluektova E, Svistushkin V, Sobolev V, Shifrin O, Guarner F, Ivashkin V

MINIREVIEWS

- 1220** Emerging role of colorectal mucus in gastroenterology diagnostics
Nooredinvand HA, Poullis A
- 1226** Similarities, differences, and possible interactions between hepatitis E and hepatitis C viruses: Relevance for research and clinical practice
Marascio N, Rotundo S, Quirino A, Matera G, Liberto MC, Costa C, Russo A, Trecarichi EM, Torti C

ORIGINAL ARTICLE

Basic Study

- 1239** Spinal anesthesia alleviates dextran sodium sulfate-induced colitis by modulating the gut microbiota
Hong Y, Zhao J, Chen YR, Huang ZH, Hou LD, Shen B, Xin Y
- 1257** Microbiologic risk factors of recurrent choledocholithiasis post-endoscopic sphincterotomy
Li Y, Tan WH, Wu JC, Huang ZX, Shang YY, Liang B, Chen JH, Pang R, Xie XQ, Zhang JM, Ding Y, Xue L, Chen MT, Wang J, Wu QP

Retrospective Study

- 1272** Epidemiological, clinical, and histological presentation of celiac disease in Northwest China
Wang M, Kong WJ, Feng Y, Lu JJ, Hui WJ, Liu WD, Li ZQ, Shi T, Cui M, Sun ZZ, Gao F

LETTER TO THE EDITOR

- 1284** Near-infrared fluorescence imaging guided surgery in colorectal surgery
Bae SU

ABOUT COVER

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Retrospective Study

Epidemiological, clinical, and histological presentation of celiac disease in Northwest China

Man Wang, Wen-Jie Kong, Yan Feng, Jia-Jie Lu, Wen-Jia Hui, Wei-Dong Liu, Zi-Qiong Li, Tian Shi, Mei Cui, Zhen-Zhu Sun, Feng Gao

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Abstract

BACKGROUND

Research on celiac disease (CD) in northwest China is still in its infancy. At present, large-sample data on the epidemiological, clinical, and pathological characteristics of CD are limited.

AIM

To investigate the epidemiological, clinical, and pathological characteristics of CD in northwest China.

METHODS

The clinical data of 2884 patients with gastrointestinal (GI) symptoms were retrospectively analyzed. Total immunoglobulin A (IgA) and anti-tissue transglutaminase (tTG) IgA levels were examined in all patients. Gastroscopy and colonoscopy were performed in patients with positive anti-tTG IgA and deficient total IgA levels. Atrophy of the duodenal and ileal villi was examined and histopathological examinations were performed. The modified Marsh-Oberhuber classification system was used to grade villous atrophy in the duodenum or distal ileum. The patients' *Helicobacter pylori* (*H. pylori*) infection status was compared in terms of clinical presentation and Marsh grade. Statistical analyses were performed using the t-test or chi-square test.

RESULTS

Among the 2884 patients, 73 were positive for serum anti-tTG IgA, and 50 were diagnosed with CD. The CD detection rate was significantly higher in Kazakhs

(4.39%) than in Uyghurs (2.19%), Huis (0.71%), and Hans (0.55%). The main symptoms of CD were chronic diarrhea, anorexia, anemia, fatigue, weight loss, sleep disorders, osteopenia, and osteoporosis. The body mass index of patients with CD was significantly lower than that of patients without CD. A total of 69 patients with positive serum anti-tTG IgA and two patients with deficient total IgA levels underwent GI endoscopy. Endoscopy revealed crypt hyperplasia and/or duodenal villous atrophy, mainly manifested as nodular mucosal atrophy, grooves, and fissures. The difference in *H. pylori* infection rates was not statistically significant between CD and non-CD patients but was significantly different among CD patients with different Marsh grades.

CONCLUSION

Among the patients with GI symptoms in northwestern China, the prevalence of CD was more in the Uyghur and Kazakh populations. *H. pylori* infection may be associated with CD severity.

Key Words: Celiac disease; Epidemiology; Gastrointestinal symptoms; Pathology; *Helicobacter pylori* infection

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Core Tip: Celiac disease (CD) is an autoimmune disease caused by the ingestion of gluten in genetically susceptible individuals. The global prevalence of CD is approximately 1.4%. An increase in celiac-specific autoantibody levels can lead to varying degrees of damage to the small intestinal mucosa and consequently to various gastrointestinal and systemic symptoms. This study reports the epidemiological, clinical, and pathological characteristics of CD and its association with *Helicobacter pylori* infection and aims to provide useful information for the clinical diagnosis and treatment of CD.

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INTRODUCTION

Celiac disease (CD) is an autoimmune chronic inflammatory disorder of the small intestine caused by ingestion of gluten in genetically susceptible individuals. Intestinal mucosal gluten-reactive CD4⁺ T cells are involved in the pathogenesis of CD[1]. The presence of T-cells in the mucosa can cause varying degrees of damage to the small intestinal mucosa, leading to a variety of gastrointestinal (GI) and systemic symptoms[2]. Typical GI manifestations include abdominal pain, abdominal distension, and diarrhea, whereas non-GI manifestations include anemia, osteoporosis, herpetic dermatitis, and neurological symptoms[3,4]. Early epidemiological studies have suggested that CD is common in Caucasian populations, particularly in Europe and North America[5,6]. Several studies in other regions have shown similar CD prevalence rates in the Middle East, Asia, Southeast Asia, and Oceania (0.2%–1%)[7-9]. The global prevalence of CD is approximately 1.4%, which is gradually increasing[9,10]. The prevalence of CD among hospitalized patients has also been investigated. A report from Brazil found that the prevalence of CD was 1.9% among 1030 hospitalized patients[11]. The detection rate of CD was 4.48% in patients with irritable bowel syndrome[12].

There are scarce data on the prevalence of CD in Asia, while no data have been compiled for some countries. The prevalence of CD among asymptomatic adults in Japan is 0.05%, and no study has investigated the prevalence of CD in Japanese children[13]. The prevalence of CD in Indian children is approximately 1%[14]. In Central Asia, the prevalence of HLA-DQ alleles susceptible to CD is similar to that in Europe; however, epidemiological and clinical studies are lacking[15]. The seropositivity for CD in the Chinese population is mainly concentrated in the northern region. A meta-analysis reported that the CD seroprevalence in the general population in China was 0.27%, whereas the CD seroprevalence in the high-risk population was 8.34%[16]. According to a study screening 118 Chinese children with chronic diarrhea, 14 patients were subsequently diagnosed with CD[17]. Research on CD in China is still in its infancy, with only a few cases reported[17,18]. However, the presence of CD susceptibility genes is not uncommon among the Chinese population, and it is believed that the actual number of CD cases in China may be much higher than the currently reported number of diagnosed cases[19].

Serum endomysium antibodies (EMAs) and antibodies against tissue transglutaminase (tTG) are commonly used serological tests for CD. Studies have shown that the sensitivity and specificity of anti-tTG immunoglobulin A (IgA) were 92.5% and 97.9%, respectively. Though EMA IgA testing is less sensitive, it is more specific than anti-tTG IgA, with sensitivity and specificity of 79.0% and 99.0%, respectively[20]. Anti-tTG IgA is the standard test used to screen for CD, while EMA IgA is widely used to confirm the diagnosis. Human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 genotyping can be used to exclude CD[21,22]; however, these are poor diagnostic tests because not all individuals with these genetic variations develop CD. Duodenal mucosal biopsy remains the gold standard for diagnosing CD, and characteristic changes include villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis. Therefore, specific serum antibody testing and endoscopic duodenal mucosal biopsy should be performed for patients with suspected CD[23,24].

The clinical presentation of CD is both complex and diverse. However, the diagnosis and treatment of CD is relatively simple. A strict gluten-free diet (GFD) is the most effective dietary intervention for disease control, but it has some limitations. Clinical trials of other non-dietary therapies are currently underway. However, owing to the lack of understanding of the disease, identification of high-risk populations for CD remains a challenge, which leads to high rates of missed diagnoses of early-stage CD, resulting in patients frequently developing serious complications.

Northwest China is a multiethnic region with ethnic groups such as Hans, Uyghurs, Huis, and Kazakhs. People living in this area have similar eating habits, with wheat being the staple food crop. In addition, this region is located in Central Asia and geographically close to Europe, where the incidence of CD is high. Genetic exchanges may have occurred between residents and travelers on the ancient Silk Road in this region. Therefore, many cases of CD may remain undiagnosed in this geographical area owing to insufficient knowledge of the disease. This study explored the prevalence, clinical manifestations, and pathological characteristics of CD in northwest China with the aim of improving clinician awareness of the disease, reducing the rates of missed diagnoses and misdiagnoses, and improving patients' quality of life.

MATERIALS AND METHODS

Patient and public involvement

This retrospective cross-sectional study was conducted in the Department of Gastroenterology of the People's Hospital of Xinjiang Uygur Autonomous Region. The study was approved by the hospital's institutional review board (IRB) (Register number: KY2021052611). All patients who underwent gastroduodenoscopy signed an informed consent form, and the IRB waived the requirement for informed consent for other clinical data. This study was conducted in adherence to STROBE guidelines.

Inclusion and exclusion criteria

The clinical data of 3147 patients, including adults and children, with GI symptoms, such as chronic diarrhea, abdominal pain, abdominal distension, constipation, vomiting, nausea, anorexia, heartburn, acid reflux, and burping, were collected from both inpatient and outpatient services between March 2016 and February 2021. All included patients agreed to undergo tests for CD and all relevant clinical data were kept confidential. To investigate the incidence of ileal villous atrophy and exclude diseases other than CD, anti-tTG IgA-positive patients were further examined using gastroduodenoscopy. Colonoscopy with ileal biopsy was not mandatory for the diagnosis of CD. The exclusion criteria were as follows: Physically healthy patients without GI symptoms; patients with digestive tract tumors or a history of other cancer types; patients with a history of cholecystectomy or gastric, duodenal, colon, or small intestinal surgery; and patients with liver cirrhosis, hepatitis, or acquired immunodeficiency syndrome.

Chronic diarrhea was defined as diarrhea lasting for > 4 wk, or recurrent diarrhea with an intermittent period of 2–4 wk. Anemia was defined as hemoglobin (Hb) levels < 110 g/L in children aged 6 months to 6 years, < 120 g/L in children aged 6–14 years, < 130 g/L in adult men, and < 120 g/L in adult women. Bone mineral density was measured using dual energy X-ray absorptiometry, with T-scores of -2.5 to -1 defined as osteopenia and T-scores of ≤ -2.5 defined as osteoporosis. Weight loss was defined as an unexplained reduction of > 5% in initial body weight within 6 mo. Anxiety and depression were quantified using the Hamilton Anxiety Rating Scale and Hamilton Depression Rating Scale, respectively. General patient information including sex, age, race, body mass index (BMI), GI signs and symptoms, comorbidities, *Helicobacter pylori* (*H. pylori*) infection status, and GI endoscopy and pathology results were collected.

Serological tests

Approximately 3–5 mL of venous blood was drawn from each patient, centrifuged to separate the serum, aliquoted, and frozen at -70 °C until required. Serum total IgA was evaluated using the immunoturbidimetric method, with levels of < 0.82 g/L considered as absence of selective IgA. Anti-tTG IgA levels were measured in patients with normal total IgA levels using enzyme-linked

immunosorbent assays, with anti-tTG IgA levels > 20 CU defined as positive. Testing was conducted in accordance with the kit instructions, and the test kit was sourced from INOVA Diagnostics Inc. (United States). Patients positive for anti-tTG IgA and total IgA deficiency underwent GI endoscopy.

Endoscopic, histological assessments and *H. pylori* infection

GI endoscopy was performed using an Olympus endoscope (Olympus EVIS LUCERA CV290, Tokyo, Japan). The mucosa of the duodenal bulb, descending duodenum, and terminal ileum were observed using white-light endoscopy. Villous architecture was further observed by near-focus narrow-band imaging, the water immersion method, and indigo carmine staining. Pathological biopsies were performed on the duodenal bulb (two pathological tissue samples), descending duodenum (four pathological tissue samples), and terminal ileum (two pathological tissue samples). Two blinded pathologists made the histopathological diagnoses and graded villous atrophy in the duodenum or distal ileum according to the modified Marsh-Oberhuber classification system[25]. Disagreements in the classification and grading were resolved by consensus. CD was diagnosed when the biopsy result was classified as Marsh grade ≥ 2 .

For histological diagnosis of *H. pylori* infection, biopsy specimens were obtained from the antrum, corpus, and angulus of the stomach. Hematoxylin-eosin and Giemsa staining was performed as appropriate. *H. pylori* infection was considered negative if *H. pylori* was absent in all biopsy sites and positive if *H. pylori* was present in at least one biopsy site. If the histological diagnosis of *H. pylori* infection was negative, but the urea breath test showed positive results, the patient was diagnosed with *H. pylori* infection.

Statistical analysis

The SPSS software (version 17.0) was used for all statistical analyses. Normally distributed continuous data were compared using the t-test and are presented as mean \pm SD, whereas categorical data were compared using the chi-square or Fisher's exact test and are presented as numbers and percentages. Statistical significance was set at $P < 0.05$.

Data availability

The datasets used and/or analyzed during the study are available from the corresponding author upon reasonable request.

RESULTS

Epidemiological characteristics

Of the 3147 patients with GI symptoms, such as chronic diarrhea, abdominal pain, abdominal distension, and weight loss, 2884 met the inclusion criteria (Figure 1). The participants, with ages ranging from 2 to 96 years, were divided into categories according to age. The majority of subjects fell within the 40-59 years, and ≥ 60 years age groups (34.3% and 30.7%, respectively). There were 1531 men (53.1%) and 1353 women (46.9%). When patients were grouped by ethnicity, 1097 (38.0%) were Hans, 1048 (36.3%) were Uyghurs, 387 (13.5%) were Kazakhs, 283 (9.8%) were Hui, and 69 (2.4%) were of other ethnicities. Table 1 summarizes the incidence of CD based on ethnic group, sex, age group, and BMI, and the correlation analysis results for each variable. Among these factors, there were significant associations based on ethnicity ($P < 0.05$) and BMI ($P < 0.01$). In terms of ethnicity, CD incidence was lowest in Hans (0.55% in Hans, 2.19% in Uyghurs, 4.39% in Kazakhs, and 0.71% in Huis). Among the other ethnicities, one Mongolian and one Uzbek patient were diagnosed with CD; however, this was not analyzed further because of the small sample size. All participants were tested for total serum IgA and anti-tTG IgA levels. Overall, two IgA-deficient patients and 73 anti-tTG IgA-positive patients were identified. The rate of positive serum anti-tTG IgA level was 2.53%. A total of 71 patients underwent GI endoscopy: Two IgA-deficient patients and 69 anti-tTG IgA-positive patients. Pathological classification was performed according to the modified Marsh-Oberhuber classification (Table 2). Two patients with total IgA deficiency had Marsh grades of 0. Among the 69 patients, 10 had Marsh grade 0, 9 had Marsh grade 1, and 50 had Marsh grade ≥ 2 . Patients with Marsh grades 0 and 1 were excluded, and 50 patients with Marsh grade ≥ 2 were eventually diagnosed with CD. The overall CD detection rate was 1.73%.

Clinical signs and symptoms

CD was more common in patients with a BMI ≤ 18.49 kg/m² (5.50%). No significant differences were noted in CD incidence when patients were evaluated based on age or sex. The incidence rates for abdominal pain in non-CD and CD patients were 50.7% and 54.0%, respectively, and abdominal distension were 49.4% and 58.0%, respectively. The rates of chronic diarrhea, anorexia, anemia, fatigue, weight loss, sleep disorders, osteopenia, and osteoporosis were significantly higher in patients with CD than in those without CD. No significant differences were noted in the incidence of constipation, vomiting and/or nausea, heartburn and/or acid reflux, belching, headache and/or dizziness, anxiety

Table 1 General information of included subjects

Subjects, <i>n</i> (%)			Coeliac disease	Frequency	95%CI	<i>P</i> value
Ethnicity						
Han	1097	38.0	6	0.55	0.1-1.0	< 0.001
Uygur	1048	36.3	23	2.19	1.3-3.1	
Kazakh	387	13.5	17	4.39	2.3-6.4	
Hui	283	9.8	2	0.71	0.0-1.7	
Others	69	2.4	2	2.90	0.0-7.0	
Gender						
Male	1531	53.1	22	1.44	0.8-2.0	0.202
Female	1353	46.9	28	2.07	1.3-2.8	
Age						
0-19	283	9.8	3	1.06	0.0-2.3	0.135
20-39	727	25.2	16	2.20	1.1-3.3	
40-59	989	34.3	22	2.22	1.3-3.1	
≥ 60	885	30.7	9	1.02	0.4-1.7	
BMI						
≤ 18.49	159	5.5	14	8.81	4.4-13.3	< 0.001
18.5-23.99	1237	42.9	23	1.86	1.1-2.6	
24-27.99	1064	36.9	7	0.66	0.2-1.1	
≥ 28	424	14.7	6	1.42	0.3-2.5	
Total	2884	100.0	50	1.73	1.3-2.2	

Table 2 The modified Marsh–Oberhuber classification[24]

	Marsh 0	Marsh 1	Marsh 2	Marsh 3			Marsh 4 ²
				3a	3b	3c	
IEL count ¹	< 30/100	> 30/100	> 30/100	> 30/100	> 30/100	> 30/100	< 30/100
Crypt hyperplasia	-	-	+	+	+	+	-
Villous atrophy	-	-	-	Mild	Moderate	Total	Total
	Pre-infiltrative	Infiltrative	Infiltrative-hyperplastic	Flat destructive			Atrophic-hypoplastic

¹Number of intraepithelial lymphocytes *per* 100 enterocytes.²This category is principally included for historic purposes.

IEL: Intraepithelial lymphocytes.

and/or depression, or *H. pylori* infection between the CD and non-CD patients (Table 3).

Histological presentation

The main endoscopic manifestations of duodenal villous atrophy in patients with CD are nodular mucosal atrophy, grooves, and fissure-like lesions. Overall, 24 patients showed nodular mucosal atrophy, 29 showed grooves and fissure-like lesions, 4 showed mosaic signs, 12 showed scallop-like lesions, 9 showed wrinkle reduction or disappearance, and 15 showed multiple manifestations. Villous atrophy in the terminal ileum was observed in 10 patients with CD, whereas normal terminal ileal mucosa was observed in 40 patients. The histological findings of CD included total villous atrophy, increased intraepithelial lymphocytes, and crypt hyperplasia.

H. pylori infection

The *H. pylori* infection rates in CD and non-CD patients were 48.0% and 57.4%, respectively, and the

Table 3 General clinical symptoms and frequency of coeliac disease

Symptoms ¹	Subjects without coeliac disease (n = 2834), n (%)		Coeliac disease (n = 50), n (%)		P value	Total (n = 2884), n (%)		Frequency of coeliac disease among patients with symptoms (95%CI)	P value
Chronic diarrhea	258	9.1	21	42.0	< 0.001	279	9.7	7.53 (4.4-10.6)	< 0.001
Abdominal pain	1437	50.7	27	54.0	0.644	1464	50.8	1.84 (1.2-2.5)	
Abdominal distension	1400	49.4	29	58.0	0.228	1429	49.5	2.03 (1.3-2.8)	
Constipation	397	14.0	5	10.0	0.417	402	13.9	1.24 (0.2-2.3)	
Anorexia	640	22.6	20	40.0	0.004	660	22.9	3.03 (1.7-4.3)	
Vomit or/and nausea	802	28.3	18	36.0	0.231	820	28.4	2.20 (1.2-3.2)	
Heartburn or/and acid reflux	740	26.1	12	24.0	0.736	752	26.1	1.60 (0.7-2.5)	
Belch	776	27.4	13	26.0	0.828	789	27.4	1.65 (0.8-2.5)	
Headache or/and dizziness	677	23.9	14	28.0	0.500	691	24.0	2.03 (1.0-3.1)	
Anemia	416	14.7	20	40.0	< 0.001	436	15.1	4.59 (2.6-6.6)	
Fatigue	536	18.9	24	48.0	< 0.001	560	19.4	4.29 (2.6-6.0)	
Weight loss	873	30.8	24	48.0	0.009	897	31.1	2.68 (1.6-3.7)	
Osteopenia or osteoporosis	329	11.6	38	76.0	< 0.001	367	12.7	10.35 (7.2-13.5)	
Sleep disorder	771	27.2	23	46.0	0.003	794	27.5	2.90 (1.7-4.1)	
Anxiety and depression	808	28.5	17	34.0	0.395	825	28.6	2.06 (1.1-3.0)	
<i>H. pylori</i> infection	1627	57.4	24	48.0	0.182	1651	57.2	1.45 (0.9-2.0)	

¹Note that patients had more than one symptom.

difference was not statistically significant. Abdominal pain was significantly more frequent in patients with CD without *H. pylori* infection than in those with *H. pylori* infection. Of the 50 patients diagnosed with CD, 17 were classified as having Marsh grade 2 and 33 as having Marsh grade 3. The rates of *H. pylori* infection were significantly different among the different Marsh grades ($P = 0.032$) (Table 4). Further pairwise comparisons showed significant differences in the detection rate of *H. pylori* between CD patients with Marsh grades 2 and 3b ($P = 0.025$). Patients with *H. pylori* infection were more commonly found to have Marsh grade 2, and more patients without *H. pylori* had Marsh grade 3b.

DISCUSSION

Currently, there is a paucity of clinical and epidemiological data on CD in China. To the best of our knowledge, to date, no large-sized sample data analysis of the pathological characteristics of patients with CD is available in the literature. Additionally, there have been no published reports on the relationship between CD and *H. pylori* infection. The prevalence of CD is high in Europe[9,26]. Northwest China connects Eurasia and lies on the ancient Silk Road. Historically, owing to the possibility of intermarriages between the populations of the two regions, there may have been transfer of CD susceptibility genes present in European populations to this region, leading to an increase in CD incidence. In addition to genetic susceptibility, wheat is the main food crop for this population. These factors may have contributed to the high detection rate of CD in northwest China. Northwest China is a multi-ethnic region in which ethnic groups such as Hans, Uyghurs, Huis, and Kazakhs live together. A previous study by Zhou *et al*[27] found a higher incidence of CD in Xinjiang and a higher detection rate of CD in Kazakhs than in Uyghurs and Hans[27]. Studies have found that HLA-DQ2 and HLA-DQ8 gene carrier rates are high in Kazakhs and Uyghurs[27,28]. Genetic susceptibility may be the reason for the difference in prevalence among different races.

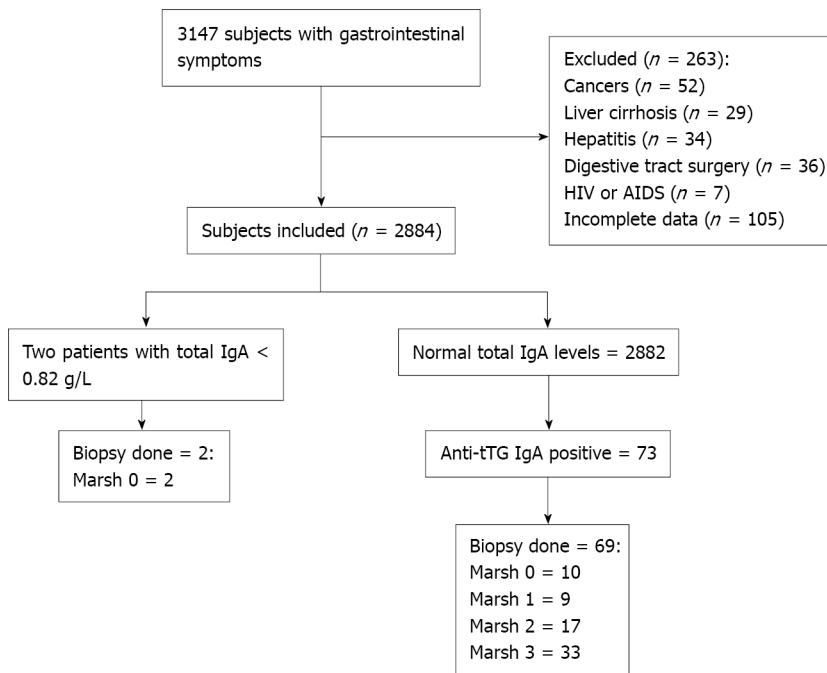
Table 4 Clinical signs and symptoms, celiac grading according to the presence of *Helicobacter pylori* in celiac disease patients

Symptom, sign, associated condition or, test	HP (+) (n = 24)	HP (-) (n = 26)	OR (95%CI)	P value
Chronic diarrhea	12 (50.0)	9 (34.6)	1.89 (0.61-5.89)	0.271
Abdominal pain	17 (70.8)	10 (38.5)	3.89 (1.19-12.68)	0.022
Abdominal distension	15 (62.5)	14 (53.8)	1.43 (0.46-4.42)	0.536
Constipation	4 (16.7)	1 (3.8)	5.0 (0.52-48.34)	0.182
Anorexia	8 (33.3)	12 (46.2)	0.58 (0.19-1.84)	0.355
Vomit or/and nausea	11 (20.8)	7 (50.0)	2.30 (0.71-7.45)	0.164
Heartburn or/and acid reflux	8 (33.3)	4 (15.4)	2.75 (0.70-10.74)	0.138
Belch	6 (25.0)	7 (26.9)	0.91 (0.26-3.21)	0.877
Headache or/and dizziness	5 (20.8)	9 (34.6)	0.50 (0.14-1.78)	0.278
Anemia	8 (33.3)	12 (46.2)	0.58 (0.19-1.84)	0.355
Fatigue	11 (45.8)	13 (50.0)	0.85 (0.28-2.57)	0.768
Weight loss	10 (41.7)	14 (53.8)	0.61 (0.20-1.88)	0.389
Osteopenia or osteoporosis	20 (83.3)	18 (69.2)	2.22 (0.57-8.65)	0.243
Sleep disorder	11 (45.8)	12 (46.2)	0.99 (0.32-3.01)	0.982
Anxiety or/and depression	6 (25.0)	11 (42.3)	0.46 (0.14-1.52)	0.197
Celiac grading, No. (%)				0.032
Marsh grade 2 (n = 17)	12 (50.0)	5 (19.2)	1.0 (ref)	
Marsh grade 3a (n = 16)	6 (25.0)	10 (38.5)	0.25 (0.06-1.07)	
Marsh grade 3b (n = 13)	3 (12.5)	10 (38.5)	0.13 (0.02-0.66)	
Marsh grade 3c (n = 4)	3 (12.5)	1 (3.8)	1.25 (0.10-15.11)	

Patients may have one or more associated symptoms or conditions.

In this study, 2884 patients with GI symptoms were screened for CD according to the global guidelines of the World Gastroenterology Organization[29]. Among them, 73 were positive for anti-tTG IgA and 50 were pathologically diagnosed with CD. CD can occur at any age, and the prevalence rate in women is 2–4 times higher than that in men[30,31]. In line with this, our study found a higher prevalence of CD in female patients than in male patients. The clinical manifestations of CD include delayed growth, malnutrition, chronic diarrhea, abdominal pain, and abdominal distension. Up to 17% of female patients may present with severe clinical manifestations during pregnancy or puerperium [32]. This study found that the main clinical manifestations of patients with CD in Xinjiang included chronic diarrhea, severe malnutrition, osteoporosis, anemia, fatigue, and decreased BMI. BMI is an important index for evaluating and predicting CD, and diarrhea is a typical symptom of CD. The immune response caused by gluten intake in susceptible populations leads to intestinal absorption dysfunction and osmotic diarrhea. In our study, 21 patients with CD-related diarrhea mainly presented with profuse watery and fatty diarrhea. Owing to the lack of knowledge and limited diagnostic criteria for CD, diarrhea often becomes chronic, making the disease more difficult to control. Therefore, most patients exhibit significant weight loss, accompanied by anemia, iron and vitamin D deficiency, and other forms of malnutrition. In Britain, individuals with suspected CD are screened to avoid complications associated with delayed CD diagnosis[24]. Therefore, CD screening should be performed in patients with GI symptoms in China, especially in those with anorexia and significant weight loss. Most patients with CD in Europe initially present with extra-intestinal manifestations and are missed because they are not tested for CD[33]. The European Society for Pediatric Gastroenterology Hepatology and Nutrition suggests that relatives of patients with CD or other autoimmune diseases should also be screened for the same conditions. Mass screening for CD is currently not recommended[3]. At present, there are no relevant guidelines for CD in the Chinese population; however, a strategy similar to that followed in Europe could be adopted.

CD is caused by gluten in susceptible subjects, however, its etiology is not fully understood. With the increasing prevalence of CD, researchers have begun to consider environmental risk factors that may trigger autoimmunity in the small intestine[34]. *H. pylori* is one of the most common chronic bacterial infections worldwide and can cause severe gastroduodenal diseases[35]. Both *H. pylori* infection and CD



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Figure 1 Flow chart of the patient enrollment. IgA: Immunoglobulin A; HIV: Human immunodeficiency virus; AIDS: Acquired immunodeficiency syndrome.

involve systemic humoral and local inflammatory immune responses. Chronic gastric infections that can induce duodenal ulcers and affect the systemic immune response may trigger autoimmunity in the small intestine[36]. Whether *H. pylori* infection can prevent or induce CD remains debatable. Epidemiological studies have investigated the association between *H. pylori* infection and CD. However, these studies reported conflicting results[37-39]. The variability in the results may be due to the different prevalence of *H. pylori* infection in different populations and the identification of patients who have not yet demonstrated clinically significant CD. There are no reports on the relationship between CD and *H. pylori* infection in northwest China.

We evaluated the relationship between *H. pylori* infection and CD and found that *H. pylori*-positive CD patients demonstrated more severe mucosal damage than *H. pylori*-negative CD patients (Marsh grades 2 and 3) ($P = 0.018$). This finding is similar to that of Gungor *et al*[40]. However, it has been reported that in individuals without CD, *H. pylori* infection itself can cause duodenal mucosal damage [41]. In a study by Konturek *et al*[42], the prevalence of *H. pylori* infection was higher in patients with CD than in controls[42]. Previous studies have shown that *H. pylori* infection can prevent the development of CD[43,44]. This association may be related to the genetic factors of CD and/or *H. pylori*, virulence of *H. pylori*, and immunopathology involved. In addition to altering the acidity and content of gastric juice, *H. pylori* directly interacts with the immune system and increases intestinal permeability [45].

In patients with CD, biopsy usually shows villous atrophy, crypt hyperplasia, and inflammation. However, some serologically positive individuals can have normal intestinal mucosa, but many of these patients later develop CD, which is sometimes termed “latent CD”[46]. In these atypical cases, more than 95% of anti-tTG IgA-positive patients may be sensitive to glutenin[47]. Our study found that the grades of five patients who presented with Marsh grade 1 in 2016–2019 improved to Marsh grade 0 on gastroscopy after following a GFD for at least half a year. Therefore, we speculate that early initiation of a GFD can improve the condition of patients with anti-tTG IgA-positive “latent CD.” The healing rates of patients often differ significantly, and the older the patient at the time of the first diagnosis, the slower the intestinal healing process and the higher the possibility of nonreactive CD. There is no relevant research on “latent CD” in China and more extensive screening and follow-up are necessary. Early diagnosis of CD can reduce the long-term and persistent damage caused by gluten to the intestinal tract and whole body, thus resulting in better patient prognosis. Common causes of CD-related deaths are intestinal non-Hodgkin’s lymphoma and small-bowel cancers[48]. Refractory CD (RCD) is a major cause of poor prognosis. RCDs can be divided into types I (RCD I) and II (RCD II). The phenotype of intraepithelial lymphocytes (IELs) is abnormal in RCD II patients and normal in RCD I patients. Approximately 50%–60% of patients with RCD II develop EATL within 5 years after diagnosis[49]. Both are (pre)malignant complications of CD. Patients with RCD II and EATL often have more severe malnutrition due to intestinal malabsorption and hypermetabolism[50]. No patients with RCD or EATL were found in this study; however, Marsh grades were positively correlated with patient age. Therefore, patients with CD who have significant weight loss or are elderly should be screened for CD using GI

endoscopy.

Study limitations

To the best of our knowledge, this is the first study to comprehensively analyze the clinical and pathological characteristics of Chinese patients with CD and evaluate the association of CD with *H. pylori* infection. Our study not only bridges the gap in relevant research in the Chinese population but also provides reference values for the diagnosis and treatment of CD. However, this study has several limitations. The subjects were patients with GI symptoms in the hospital, which may have resulted in a selection bias. HLA-DQ2 and HLA-DQ8 genotypes were not identified in our study; therefore, further research on the relationship between these genotypes and the pathological types of CD is warranted.

CONCLUSION

Among people with GI symptoms in northwest China, the prevalence of CD is higher in the Uyghur and Kazak populations. Therefore, physicians should be aware of the risk of developing CD in regional populations. *H. pylori* infection may be related to CD severity, which warrants further study.

ARTICLE HIGHLIGHTS

Research background

Research on celiac disease (CD) in Northwest China is still in its infancy. At present, large sample data on the epidemiological, clinical, and pathological characteristics of CD are limited.

Research motivation

This study reports the epidemiological, clinical, and pathological characteristics of CD and its association with *Helicobacter pylori* (*H. pylori*) infection, and aims to provide useful information for clinical diagnosis and treatment of CD.

Research objectives

To investigate the epidemiological, clinical, and pathological characteristics of CD in northwest China.

Research methods

The clinical data of 2884 patients with gastrointestinal (GI) symptoms were retrospectively analyzed. Total immunoglobulin A and anti-tissue transglutaminase (tTG) immunoglobulin A (IgA) levels were examined for all patients. Gastroscopy and colonoscopy were performed in patients with positive anti-tTG IgA and deficient total IgA levels. Atrophy of the duodenal and ileal villi was examined, and histopathological examinations were performed. The modified Marsh–Oberhuber classification system was used to grade villous atrophy in the duodenum or distal ileum. Patient *H. pylori* infection status was compared in terms of clinical presentation and Marsh grade. Statistical analyses were performed using t-test or chi-square test.

Research results

The detection rate of CD was significantly higher in Kazakhs (4.39%) than in Uyghurs (2.19%), Huis (0.71%), and Hans (0.55%). The main symptoms of CD were chronic diarrhea, anorexia, anemia, fatigue, weight loss, sleep disorders, osteopenia, and osteoporosis. The body mass index of CD patients was significantly lower than that of non-CD patients. Endoscopy revealed crypt hyperplasia and/or duodenal villous atrophy, which mainly manifested as nodular mucosal atrophy, grooves, and fissures. The difference in *H. pylori* infection rates was not statistically significant between CD and non-CD patients, but was significantly different among CD patients with different Marsh grades. Patients with *H. pylori* infection were more commonly found with Marsh grade 2 and more patients without *H. pylori* had Marsh grade 3b.

Research conclusions

Among people with GI symptoms in Northwest China, the prevalence of CD is higher in the Uyghur and Kazak populations. Physicians should be aware of the risk of CD in the regional population. *H. pylori* infection may be related to the severity of CD, which warrants further study.

Research perspectives

H. pylori infection may be related to the severity of CD, which warrants further study.

FOOTNOTES

Author contributions: Wang M and Gao F designed the study; Wang M, Kong WJ, and Lu JJ acquired the data and drafted the article; Hui WJ and Liu WD analyzed and interpreted the data; Cui M and Sun ZZ made a pathological diagnosis; Feng Y, Li ZQ, Shi T and Gao F revised the article critically for important intellectual content; all the authors approved the version to be published.

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