Turk J Gastroenterol *2016; 27: 521-4*

Screening of patients with juvenile idiopathic arthritis and those with rheumatoid arthritis for celiac disease in southwestern Iran

INTESTINE

Mozhgan Moghtaderi[1], Shirin Farjadian[1,2], Elham Aflaki[3], Naser Honar[4], Soheila Alyasin[1], Maryam Babaei[1]

[1]Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Immunology, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Rheumatology, Shiraz University of Medical Sciences, Shiraz, Iran
[4]Department of gastroenterology, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Background/Aims: Celiac disease (CD) is a common enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. It is frequently found in conjunction with other autoimmune diseases. The purpose of this study was to investigate the prevalence of CD in patients with juvenile idiopathic arthritis (JIA) and those with rheumatoid arthritis (RA) in southwestern Iran.

Materials and Methods: A total of 53 children with JIA and 55 adults with RA were enrolled. Anti-tissue transglutaminase (tTG) immunoglobulin (Ig) A serum levels were measured by performing an enzyme-linked immunosorbent assay. Patients with anti-tTG IgA serum levels of >15 U/mL were considered seropositive and subjected to upper gastrointestinal endoscopy. Duodenal biopsies were histopathologically evaluated based on the modified Marsh classification.

Results: One child with JIA (1.8%) and six adults with RA (11.3%) were positive for the anti-tTG IgA antibody, but the histopathological evaluations of the duodenal biopsies in these patients revealed no evidence of CD-related enteropathy.

Conclusion: Although the investigation of anti-tTG antibodies is widely used as a noninvasive serologic test for the initial diagnosis of CD, because of the high positive predictive value, the clinical utility of this test alone for making a diagnosis is doubtful. We found no cases of CD among our patients with JIA and RA. The periodic screening of rheumatologic patients with positive anti-tTG IgA for CD can be helpful in making an early diagnosis of CD in these patients.

Keywords: Celiac disease, juvenile idiopathic arthritis, rheumatoid arthritis, serologic tests

Original Article

INTRODUCTION

Celiac disease (CD) is a common enteropathy triggered by the ingestion of gluten in genetically susceptible individuals (1,2). Vigorous $CD4^+$ T-helper 1 cell activation has been implicated in patients with CD (3,4). The association of CD with autoimmune rheumatologic diseases such as juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA), and primary Sjögren syndrome has been reported (5-7). The coincidence of CD with some rheumatologic diseases suggests the impact of a common pathogenic autoimmune mechanism or the involvement of the same genes in the susceptibility to these diseases (3,8).

The clinical features of CD considerably vary from typical intestinal to extraintestinal symptoms without any digestive manifestations. Arthritis in peripheral and axial skeletal joints might be an early extraintestinal manifestation of CD (9). The involvement of the gastrointestinal system has also been seen in patients with rheumatologic diseases (10).

The diagnosis of CD requires at least four of the following criteria for documentation: the presence of the usual symptoms of CD including diarrhea, stunting, iron deficiency anemia, high titers of CD immunoglobulin (Ig) A and human leukocyte antigen (HLA)-DQ2 or DQ8

Address for Correspondence: Shirin Farjadian E-mail: farjadsh@sums.ac.ir
Received: June 19, 2016 **Accepted:** August 19, 2016
 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2016.16354

genotypes, celiac enteropathy on duodenal biopsy, and potential response to a gluten-free diet (11).

The risk of developing CD after diagnosing autoimmune rheumatologic diseases has been investigated in different geographic areas. Studies in Iran have reported that the prevalence rates of CD range from 0.5% to 0.9% in northern and southern Iran (12-14). This study was designed to investigate the frequency of CD in patients with JIA and RA in southwestern Iran.

MATERIALS AND METHODS

This prospective study was conducted on 53 children with JIA and 55 adults with RA from southwestern Iran who were referred to the Rheumatology Outpatient Clinics affiliated to Shiraz University of Medical Sciences in 2015. The study protocol was approved by the Ethics Committee of Shiraz University, and informed consent was obtained from patients or their parents after the study was described in detail.

Demographic data including gender; age; involvement of diabetes mellitus, hypothyroidism, and other autoimmune diseases; duration of their disease; and family history of CD and rheumatic diseases was recorded. Information about abdominal pain, chronic diarrhea, constipation, vomiting, and decreased appetite was also collected.

Using a digital scale, weight and height were measured at the time conducting the study in the children. A patient with a body mass index (BMI) less than 18.5 kg/m^2 was considered underweight (15).

Laboratory data including cell blood count (CBC), erythrocyte sedimentation rate (ESR), and aspartate transaminase (AST) and alanine transaminase (ALT) levels were determined in all patients. The total serum IgA level was measured by nephelometry, and IgA anti-tissue transglutaminase (tTG) levels were evaluated by enzyme-linked immunosorbent assay using a commercial kit (AESKU Diagnostics GmbH, Wendelsheim, Germany). Patients with anti-tTG IgA levels >15 U/mL were considered seropositive and subjected to upper gastrointestinal endoscopy. Three endoscopic mucosal biopsies were obtained from the distal duodenum, and the mucosa was morphologically graded based on the established criteria (16). Duodenal biopsies were histopathologically evaluated based on the modified Marsh classification (17).

In our study, upper endoscopy and duodenal biopsy were performed in patients with abnormal serologic results.

Statistical analysis

All data was analyzed by SPSS version 18 (SPSS Inc.; Chicago, IL, USA) Data were mentioned as mean±standard deviation (SD). To compare the results of laboratory findings between patients with JIA and those with RA, the t-test was used. A p-value less than 0.05 was considered significant.

Table 1. Frequency of celiac disease-associated symptoms in patients with JIA and those with RA

Symptoms	Number of patients with JIA n=53	Number of patients with RA n=55
Abdominal pain	4 (7.5%)	7 (12.7%)
Chronic diarrhea	0 (0.0%)	0 (0.0%)
Constipation	0 (0.0%)	8 (14.5%)
Decreased appetite	6 (11.3%)	2 (3.6%)
BMI<18.5 kg/m^2	8 (15%)	0 (0.0%)
Vomiting	0 (0.0%)	1 (1.8%)

JIA: juvenile idiopathic arthritis; RA: rheumatoid arthritis; BMI: body mass index

Table 2. Laboratory findings in patients with JIA and those with RA

Laboratory data	Patients with JIA	Patients with RA
	Mean±SD	
WBC (count/µL)	7584±3445.2	6287.5±2393.6
Hb (g/dL)	11.7±1.8	13±1.3
AST (U/L)	25±6.7	20.8±6.1
ALT (U/L)	17±7.2	20±7.5
ESR (mm/h)	19.2±14.7	20.4±12.5
Anti-tTG IgA (U/mL)	2.9±3.7	10.6±22.9

JIA: juvenile idiopathic arthritis; RA: rheumatoid arthritis; WBC: white blood cell; Hb: hemoglobin; AST: aspartate transaminase; ALT: alanine transaminase; ESR: erythrocyte sedimentation rate; tTG: tissue transglutaminase; SD: standard deviation

RESULTS

Fifty-three children (26 girls and 27 boys) ranging in age from 1.5 to 16 (mean age, 15.6±4) years, with JIA and 55 adults (40 females and 15 males), ranging in age from 20 to 75 (mean age, 46.4±13.4) years, were enrolled. The mean disease duration was 3.5±3 years in patients with JIA and 15.2±9 years in patients with RA. Diabetes mellitus and hypothyroidism were detected in seven patients with RA. Seven children and nine adults had a family history of rheumatic disease, and none of them had a family history of CD.

The frequency of CD-associated symptoms in JIA and RA is shown in Table 1. The laboratory test results of all studied patients are presented in Table 2. One child with JIA and six adults with RA were positive for the anti-tTG IgA antibody (>15 U/mL). The total serum IgA level was normal in all patients. There was a significant difference in the anti-tTG IgA level between patients with JIA and those with RA (p=0.01), with increased levels in patients with RA.

Decreased appetite and constipation were frequent CD-associated symptoms in the patients with JIA and those with RA, respectively. Small bowel mucosa was normal in six of the seven patients with a positive anti-tTG IgA antibody; one of these

Table 3. Characteristics of patients with JIA and those with RA who had positive serological findings for CD

	Patients with rheumatologic diseases						
Characteristic criteria	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Age (year)	2	69	32	46	62	64	35
Sex	F	F	F	F	F	M	F
Disease	JIA	RA	RA	RA	RA	RA	RA
Disease duration (years)	0.5	4	30	16	12	34	20
Symptoms for CD	Yes	No	No	No	Yes	Yes	No
Associated disease	No	Hypothyroidism	No	Diabetes mellitus	No	Diabetes mellitus	No
Hemoglobin (g/dL)	11.4	15.7	10.9	12.4	12.1	14.3	13.8
Anti-tTG IgA (U/mL)	19.7	25.6	55.8	27.4	120.6	52	107.4
Duodenal biopsy result	Normal	No data	Normal	Normal	Normal	Normal	Normal

JIA: juvenile idiopathic arthritis; RA: rheumatoid arthritis; CD: celiac disease; Ttg IgA: tissue transglutaminase immunoglobulin A; F: female; M: male

patients refused endoscopy. The characteristics of the seven patients with positive serological findings for CD are presented in Table 3.

DISCUSSION

Autoantibodies play essential roles in the pathogenesis of many diseases such as rheumatologic conditions and CD. Our results showed increased levels of the anti-tTG IgA antibody in 1.8% of the patients with JIA and in 11.3% of the patients with RA.

One of the most common rheumatologic diseases in children is JIA. There are some reports showing increased serological marker levels of CD in patients with JIA. George et al. (18) found high levels of anti-gliadin antibodies in 12.9% of children with JIA. Lepore et al. (19) found positive anti-endomysium antibodies in 2.5% of children with JIA. Al-Mayouf et al. (20) reported positive serologic markers for CD including anti-gliadin, anti-reticulin, and anti-endomysium antibodies in 42.8% of their patients with JIA. Gheita et al. (5) found anti-tTG antibodies (IgA and IgG) in 53.3% of children with JIA and in 20% of healthy children. The results of aforementioned studies revealed a higher prevalence of positive serological markers for CD in patients with JIA than our results. It may be explained by differences in the type of antibody used for screening, sample size, concurrent involvement with other autoimmune diseases, and genetic background of the target population.

There are a few studies on the prevalence of CD in patients with RA. Koszarny et al. (7) found the presence of anti-gliadin antibody in 4.1% of their patients with RA, which is less than what we found in our study based on presence of the anti-tTg IgA antibody.

Our results showed a higher level of the anti-tTG antibody in adults with RA than in children with JIA. Baldas et al. (21) showed an age-related increase in anti-tTg antibody titers. The coincidence of additional autoimmune diseases such as diabetes mellitus and hypothyroidism in adult patients with RA seems to play a role in the increased level of the anti-tTG antibody. It is believed that the production of anti-tTG antibodies is involved in several neurodegenerative disorders that are more likely at older ages (22,23).

There are two reports from southwestern Iran showing the presence of biopsy-proven CD in 0.6% of healthy children and 0.3% of healthy adults (13,24); however, we found no pathological evidence in favor of CD in our patients with JIA and those with RA, which can partly be explained by the small sample size of our patients. Francis et al. (25) also reported the same prevalence of CD (0.6%) in patients with RA and in the general population. The prevalence of CD in children with JIA was reported to be 1.5% in the Netherlands and 2.4% in Saudi Arabia (18,20). There are reports on normal initial intestinal biopsies in patients who were later found to develop CD (26,27).

Decreased appetite and constipation were frequent CD-associated symptoms in our patients with JIA and in those with RA. These symptoms can be the results of immobilization, prolonged inflammation, medication toxicity, and psychosocial factors due to rheumatologic diseases itself.

The histopathological evaluations of duodenal biopsies in our seropositive patients with JIA and those with RA revealed no association of CD with positive anti-tTG IgA. Although the investigation of anti-tTG antibodies is widely used as a noninvasive serologic test for the initial diagnosis of CD, because of its high positive predictive value, the clinical utility of this test alone for making a diagnosis is doubtful (28).

We found no cases of CD among our patients with JIA and those with RA. The periodic screening of rheumatologic patients with positive anti-tTG IgA for CD can be helpful in making an early diagnosis of CD in these patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Shiraz University of Medical Sciences.

Informed Consent: Written informed consent was obtained from patients and patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.M., S.F., E.A., N.H., S.A.; Design - M.M., S.F., E.A., N.H., S.A.; Supervision - M.M., S.F.; Data Collection and/or Processing - M.M., S.F., M.B.; Analysis and/or Interpretation - M.M., S.F., E.A., N.H., S.A., M.B.; Literature Review - M.M., S.F.; Writer - M.M., S.F.; Critical Review - M.M., S.F., E.A., N.H., S.A., M.B.

Acknowledgements: The authors thank the pathologists Dr. B. Geramizade and Dr. V.P. Kumar from Department of Pathology at Shiraz University of Medical Sciences for their great help.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received financial support by a grant from Shiraz University of Medical Sciences (grant number 35-5042).

REFERENCES

1. Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. World J Gastroenterol 2012; 18: 6036-59. [CrossRef]
2. Green PH, Cellier C. Celiac disease. N Engl J Med 2007; 357: 1731-43. [CrossRef]
3. Schuppan D, Junker Y, Barisani D. Celiac disease: from pathogenesis to novel therapies. Gastroenterology 2009; 137: 1912-33. [CrossRef]
4. Ventura A, Ronsoni MF, Shiozawa MB, et al. Prevalence and clinical features of celiac disease in patients with autoimmune thyroiditis: cross-sectional study. Sao Paulo Med J 2014; 132: 364-71. [CrossRef]
5. Gheita TA, Fawzy SM, Nour El-Din AM, Gomaa HE. Asymptomatic celiac sprue in juvenile rheumatic diseases children. Int J Rheum Dis 2012; 15: 220-6. [CrossRef]
6. Lerner A, Matthias T. Rheumatoid arthritis-celiac disease relationship: joints get that gut feeling. Autoimmun Rev 2015; 14: 1038-47. [CrossRef]
7. Koszarny A, Majdan M, Suszek D, Dryglewska M, Tabarkiewicz J. Autoantibodies against gliadin in rheumatoid arthritis and primary Sjögren's syndrome patients. Wiad Lek 2015; 68: 242-7.
8. Koning F. Recent insight in the pathophysiology of coeliac disease: relevance to rheumatoid arthritis. Clin Exp Rheumatol 2015; 33(Suppl 4): S8-10.
9. Chiu CL, Hearn NL, Lind JM. Development of a Risk Score for Extraintestinal Manifestations of Coeliac Disease. Medicine (Baltimore) 2016; 95: e3286. [CrossRef]
10. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular Manifestations in Rheumatoid Arthritis. Maedica (Buchar) 2010; 5: 286-91.
11. Catassi C, Fasano A. Celiac disease diagnosis: simple rules are better than complicated algorithms. Am J Med 2010; 123: 691-3. [CrossRef]
12. Rostami Nejad M, Rostami K, Emami MH, Zali M, Malekzadeh R. Epidemiology of Celiac Disease in Iran: A Review. Middle East J Dig Dis 2011; 3: 5-12.
13. Dehghani SM, Haghighat M, Mobayen A, Rezaianzadeh A, Geramizadeh B. Prevalence of celiac disease in healthy Iranian school children. Ann Saudi Med 2013; 33: 159-61.
14. Ahadi Z, Shafiee G, Razmandeh R, et al. Prevalence of celiac disease among the Iranian population: A systematic review and meta-analysis of observational studies. Turk J Gastroenterol 2016; 27: 122-8. [CrossRef]
15. Alderman H, Shekar M. Nutrition, food security, and health. In: Kliegman RM, Stanton BF, editors. Nelson Textbook of Pediatrics. 19th ed. Philadelphia, PA: Elsevier Saunders; 2011. P. 170-3. [CrossRef]
16. Thijs WJ, van Baarlen J, Kleibeuker JH, Kolkman JJ. Uodenal versus jejuna biopsies in suspected celiac disease. Endoscopy 2004; 36: 993-6. [CrossRef]
17. Zulfiqar S, Fahim A, Qureshi A, et al. Celiac disease; histopathological evaluation of endoscopic duodenal(d2) biopsies in patients. Professional Med J 2014; 21: 72-5.
18. George EK, Hertzberger-ten Cate R, van Suijlekom-Smit LW, et al. Juvenile chronic arthritis and coeliac disease in The Netherlands. Clin Exp Rheumatol 1996; 14: 571-5.
19. Lepore L, Martelossi S, Pennesi M, et al. Prevalence of celiac disease in patients with juvenile chronic arthritis. J Pediatr 1996; 129: 311-3. [CrossRef]
20. Al-Mayouf SM, Al-Mehaidib AI, Alkaff MA. The significance of elevated serologic markers of celiac disease in children with juvenile rheumatoid arthritis. Saudi J Gastroenterol 2003; 9: 75-8.
21. Baldas V, Not T, Tommasini A, et al. Anti-transglutaminase antibodies and age. Clin Chem 2004; 50: 1856-60. [CrossRef]
22. Martin A, Romito G, Pepe I, et al. Transglutaminase-catalyzed reactions responsible for the pathogenesis of celiac disease and neurodegenerative diseases: from basic biochemistry to clinic. Curr Med Chem 2006; 13: 1895-902. [CrossRef]
23. Ricotta M, Iannuzzi M, Vivo GD, Gentile V. Physio-pathological roles of transglutaminase-catalyzed reactions. World J Biol Chem 2010; 1: 181-7. [CrossRef]
24. Saberi-Firouzi M, Omrani GR, Nejabat M, Mehrabani D, Khademolhosseini F. Prevalence of celiac disease in Shiraz, southern Iran. Saudi J Gastroenterol 2008; 14: 135-8. [CrossRef]
25. Francis J, Carty JE, Scott BB. The prevalence of coeliac disease in rheumatoid arthritis. Eur J Gastroenterol Hepatol 2002; 14: 1355-6. [CrossRef]
26. Maki M, Holm K, Koslamies S, Hallstrom O, Visakorpi J. Normal small bowel biopsy followed by coeliac disease. Arch Dis Child 1990; 65: 1137-41. [CrossRef]
27. Collin P, Helin H, Maki M, Hallstrom O, Karvoven A. Follow-up of patients positive in reticulin and gliadin antibody tests with normal small-bowel biopsy findings. Scand J Gastroentrol 1993; 28: 595-8. [CrossRef]
28. Lock RJ, Stevens S, Pitcher MC, Unsworth DJ. Is immunoglobulin A anti-tissue transglutaminase antibody a reliable serological marker of coeliac disease? Eur J Gastroenterol Hepatol 2004; 16: 467-70. [CrossRef]