Original Article

Clinico-Histopathological Characteristics of Adult Patients with Celiac Disease; A Retrospective Study in Southeast Iran

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ABSTRACT

Background:
Celiac disease (CeD) is a permanent immune-mediated enteropathy triggered by gluten. Patients with CeD have various clinical features. In the present study, we aimed to evaluate the clinical, laboratory, and histopathological features of 150 patients with CeD in Zahedan, Southeast Iran.

Materials and Methods:
In a retrospective cross-sectional study, we investigated the characteristics of 150 patients with celiac in Zahedan from 2008 to 2018. In addition to the demographic characteristics of the patients, other parameters such as clinical symptoms, comorbidities, serum level of anti-tissue transglutaminase (IgA-TTG), liver function tests, and report of the intestinal biopsy were obtained from patients' recorded files. Descriptive statistics were used for the collected data.

Results:
150 patients were included in the study. 72 (48%) were males, and 78 (52%) were females. The mean (±SD) age was 28.5 (±10.69) years (range 16-82 years). The most frequent symptom was abdominal pain (38%), followed by diarrhea (32%) and nausea (30%). Iron-deficiency anemia was found in 30% of patients. Immunoglobulin A, and anti-tissue transglutaminase antibodies (IgA anti-TTG) were found in 144 (96%) patients. The results of the biopsy showed 76% with Marsh I, 10% with Marsh II, and 52% with Marsh III histological changes according to the Marsh classification.

Conclusions:
Most of our patients with CeD were oligo-symptomatic forms. It is essential for healthcare professionals to have the clinical features of patients diagnosed with CeD in their area.

Keywords: Celiac disease, Pathology, Diagnosis, Symptoms, Adult

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INTRODUCTION

Celiac disease (CeD) is an immune-mediated enteropathy affecting approximately 0.5%-3% of the worldwide general population (1-3). In Iran, a previous systematic review reported the overall prevalence of CeD was 2% and equal to or even more than the global prevalence (4). The classical features of CeD were described in 1887 as diarrhea, fatigue, and growth failure, but epidemiological studies have subsequently indicated several patterns of the disease (5). The presentations may differ from overt enteropathy to extraintestinal disorders, and the symptoms may even be silent (6). The diagnosis of CeD can sometimes be challenging because of the wide range of symptoms and signs (7). CeD seroprevalence studies suggest that the prevalence of CeD in the general population may be overestimated (8).

Diagnostic criteria should be considered by physicians in the case of CeD, including seropositivity, confirmation of intestinal biopsy for CeD, and responsiveness to a gluten-free diet (9). The active phase of CeD is associated with increased levels in serum of immunoglobulin A (IgA) autoantibodies against endomysium (IgA-EmA) and anti-tissue transglutaminase (IgA-TTG), and these antibodies are generally considered as a selection criterion for intestinal biopsy (7). Moreover, antigen-presenting cells which express HLA-DQ2 or -DQ8 present the gliadin-tissue transglutaminase complexes to the T cells and increase susceptible individuals to CeD. HLA genotyping may be used in patients with suspected patients with CeD (10). The intestinal biopsy specimen shows specific changes in the villous atrophy, crypt elongation, and mucosal structure, which are improved when gluten is removed from the diet (11).

Epidemiologic studies may provide important information with regard to timely diagnosis and appropriate treatment of CeD. In some regions, there are studies on clinical symptoms, risk factors, and comorbidities of CeD with other diseases. Ganji and colleagues (2014) conducted a study to determine demographic features and clinical symptoms of CeD in northeastern Iran and reported that CeD was found more frequently in women and with non-diarrheal presentations (12). Also, Ganji et al. performed a cohort study in northeastern Iran (2021) and reported that the main symptoms were dyspepsia (35.23%), diarrhea (18.52%), anemia (12.75%), growth failure (9.92%), and weight loss (8.80%). In addition, the study found that nerve problems were common comorbidities (57.43%) in CeD (13). Fanaeian et al. also reported a higher prevalence of headaches and migraine in CeD, gluten sensitivity, and inflammatory bowel disease (IBD) (ulcerative colitis) than in the control group (14).

Screening programs within general populations demonstrated that CeD is underdiagnosed (15). Adult patients with CeD tend to remain silent and have milder forms (16). However, the increased risk of autoimmune diseases and malignancies in individuals with CeD, resulting in a higher risk of morbidity and mortality, indicated screening on a low degree of suspicion, and the disease needs to be treated even in asymptomatic cases (17). Until recent decades, CeD was presumed a very rare disease in the Middle Eastern region (1). However, more recently, screening tests have diagnosed many silent and subclinical CeD (18). To the best of our knowledge, few data have been available about the epidemiological features of CeD in southeastern Iran, Zahedan. The aim of this study was to investigate the clinical picture of diagnosed CeD in this area.

MATERIALS AND METHODS

In a cross-sectional study, we retrospectively studied the characteristics of 150 patients with CeD that refer to Gastroenterology Clinics in Zahedan from March 2008 to February 2018. Informed consent was not applicable in our retrospective design research. The patients' data were collected anonymously, and no patients were involved in our study process.

All included patients had CeD, based on a positive serological (anti-tissue transglutaminase-A) and histological examination of the second part of the duodenum (any Marsh classification) and complete disappearance of symptoms after the introduction of a gluten-free diet. The important point was to determine that in patients with a Marsh type 1 lesion, the diagnosis was confirmed by the presence of characteristic small bowel mucosal changes after a gluten-free diet. Patients with incomplete documented files and doubting the diagnosis due to a lack of clinical or histological recovery with a gluten-free diet were excluded. In addition to demographic

characteristics of the patients, other parameters such as clinical symptoms, comorbidities, serum level of anti-tissue transglutaminase (IgA-TTG), complete blood count, thyroid function test, and liver function tests as well as pathologic reports of duodenal biopsies were obtained from file records of patients in the study.

Histopathological examinations were reported according to the Marsh classification; the infiltrative phase with more than 30 lymphocytes per 100 enterocytes was Marsh type I, the infiltrative/hyperplastic phase was Marsh II, and Marsh IIIA, IIIB, and IIIC were partial, subtotal, and total villous atrophy, respectively.

Collected data were coded, analyzed, and computed using SPSS software version 18. Simple statistics such as frequency and percentages, mean, and standard deviation were calculated for the different variables. Data were presented as the N (%) and mean ± SD.

RESULTS

Out of 150 patients in the study, 72 (48%) were males, and 78 (52%) were females. The mean (±SD) age was 28.5 (±10.69) years (range 16-82 years). There was no statistically meaningful difference based on sex. The most frequent symptom was abdominal pain (38%), followed by diarrhea (32%), nausea (30%), and dyspepsia (14.6%). Iron-deficiency anemia was found in 30% of the patients. One patient presented celiac crisis (0.6%). The frequency of clinical findings is shown in Table 1, and comorbidities of patients' CeD are presented in Table 2. Hypothyroidism (15%) and hypertransaminasemia (15%) were the most frequently recognized comorbidities.

Immunoglobulin A, and anti-tissue transglutaminase antibodies (IgA Anti-TTG) were found in 144 cases (96%). Biopsy of the small intestine revealed that 100% of patients had typical lesions according to the Marsh classification. Table 3 summarizes the frequency of IgA Anti-TTG and histopathological Marsh grading of intestinal biopsies. The results of the biopsy showed 76% with mild (Marsh I, II, and IIIA) and 24% with severe (Marsh IIIB, IIIC) histological changes. Histologic analysis of seronegative CeD patients revealed Marsh 3A in one patient, Marsh 3B in two patients, and Marsh 3C in three patients.

Table 1. Frequency of clinical findings of patients with celiac disease (N = 150).

	No. of patients	%
Abdominal Pain	57	38
Diarrhea	48	32
Flatulence	54	36
Nausea	45	30
GERD	30	20
Vomiting	12	8
Constipation	9	6

GERD, gastroesophageal reflux disease.

Table 2. Frequency of comorbidities in patients with celiac disease (N = 150).

	No. of patients	%
Hypothyroidism	15	10
Hypertransaminasemia	15	10
NAFLD	12	8
Diabetes type 1	12	8
Severe emaciation	6	4
Cryptogenic cirrhosis	4	2.6
IBD	3	2
Celiac crisis	1	0.6
Infertility	1	0.6

GRED, gastroesophageal reflux disease; IBD, inflammatory bowel disease; NAFLD, non-alcoholic fatty liver disease.

Table 3. Frequency of paraclinical assessment in patients with celiac disease (N = 150).

	No. of patients	%
IgA Anti-TTG (U/mL)		
Negative	6	4
Positive	144	96
Histopathological classification		
Marsh I	57	38
Marsh II	15	10
Marsh 3A	42	28
Marsh 3B	15	10
Marsh 3C	21	14

IgA Anti-TTG, IgA anti-tissue transglutaminase; U/mL, unit per milliliter.

DISCUSSION

With the availability of serologic tests, the rate of detection of CeD is increasing worldwide, and there has been a substantial change in the mode of presentation of patients with CeD. Indeed, classic or full-blown mal-absorptive syndrome presentation of CeD (steatorrhea, weight loss, and generalized edema) is relatively rare, and most patients present with none or subtle symptoms.

We evaluated the features of 150 adult patients with CeD. Most of our patients with CeD were oligo-symptomatic forms. Diarrhea with or without malabsorption syndrome is considered the classical presentation of CeD (19). In the present study, about 30% of the patients presented with chronic diarrhea, consistent with the result of the Masjedizadeh et al. study that found the most common symptom in patients with CeD in the south of Iran (diarrhea was 78.8%) (20). Ehsani-Ardakani et al., in a retrospective study from 2009 to 2011, investigated the prevalence of gastrointestinal and non-gastrointestinal symptoms in patients with CeD in Italy and Romania (Europe), and Iran and found that European patients complained of upper abdominal symptoms such as abdominal pain and dyspepsia, whereas diarrhea and abdominal distension were the most common primary complaints in Iranian patients. Anemia was also the most common complaint in both European and Iranian patients, although it was significantly higher in Iranian patients (21).

A study performed in Turkey reported the most common symptom (81.7%) of patients with CeD was diarrhea (22). The epidemiological changes in the presentation of CeD and age-related clinical features have been described both in children and adults, and mild symptoms such as abdominal pain and hypertransaminasemia are more common in adults and older children (23). Another inconsistent finding in our result was no difference based on sex (48% males and 52% female). In most of the published papers, CeD prevalence was reported higher in women (2).

Multiple pieces of evidence indicate CeD is significantly associated with various extraintestinal presentations (24,25). Our results showed iron-deficiency anemia, hypothyroidism, type 1 diabetes mellitus, and hypertransaminasemia were frequently comorbidities observed. In terms of comorbidities with CeD, our findings were in accordance with previous studies. Alavi Moghaddam and colleagues concluded in their study that CD might be associated with hypertransaminasemia in the absence of other possible causes of liver dysfunction and that clinicians need to consider the diagnosis of CeD. Moreover, this secondary hypertransaminasemia to CeD can improve with a gluten-free diet (26). Iron-deficiency anemia is often detected in new cases diagnosed with CeD and may continue for various periods after removing gluten from the diet. Iron absorption decreased in untreated CeD, especially in patients who are already affected by iron deficiency. Iron deficiency has generally been related to a declined absorption surface, particularly in the proximal small bowel (27). CeD is also accompanied by several autoimmune comorbidities. Previous epidemiological studies have reported that hypothyroidism and type 1 diabetes mellitus were the most prevalent autoimmune diseases in patients with CeD (28). The prevalence of CeD among patients with autoimmune thyroid disease has been estimated to range from 2% to 7%. CeD has been found in patients with type 1 diabetes mellitus, with a prevalence of approximately 4% (28). A systematic review reported an enhanced risk of CeD in patients with IBD and an enhanced risk of IBD in patients with CeD in comparison with other patient groups (29).

Our data also show 96% and 100% of our sample was seropositive and confirmed diagnosis for CeD with intestinal biopsy, respectively. Serologic tests are initially suggested as the first stage of diagnosis when there is a clinical presentation of CeD or suspicion in order to decide which patient should undergo intestinal biopsy. However, when the clinician has a strong suspicion for CeD, small bowel biopsies should be performed even in seronegative patients (30).

The limitations of our study were the lack of the test for HLA-DQ2/DQ8 from a genetic standpoint and the evaluation of osteopenia and micronutrient status of our patients. Future researchers are suggested to perform studies on finding silent cases and screening of at-risk groups, for instance, first-degree relatives of patients with CeD and patients with other autoimmune diseases.

CONCLUSION

Almost all of our patients with CeD were oligo-

symptomatic forms. It is essential for health care professionals to have a low threshold for test performing of CeD. In our opinion, a significant number of patients with CeD are living and dying of celiac without proper diagnosis, and this condition is potentially dangerous and can lead to a poor outcome. Silent presentation of CeD should be considered and may account for several chronic health issues.

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COMPETING INTERESTS

The authors declare no conflict of interest related to this work.

ETHICAL APPROVAL

The present study was completed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research established by the Ministry of Health and Medical Education and the Ministry of Science, Research, and Technology, Iran. We obtained approval from the Ethics Review Committee of Zahedan University of Medical Sciences, Iran (Registration No.IR.ZAUMS.REC.1392.1063).

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