



Original Article

Epidemiological, Endoscopic, Clinical, and Pathological Features of Patients with Celiac Diseases in Southern Littoral of Caspian Sea

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Abstract

Background: Celiac disease is an autoimmune disorder resulting from gluten consumption in genetically predisposed individuals. The present study investigated the epidemiological, endoscopic, and clinicopathological features of patients with celiac disease in the southern littoral of the Caspian Sea.

Methods: 140 patients with celiac disease were interviewed and examined regarding demographic characteristics, clinical symptoms, and serologic, endoscopic, and pathological findings.

Results: 44 (31.4%) of the patients were male and 68.6% were female. The mean age of the patients at diagnosis was 27.13 ± 13.4 years (ranging from 2 to 60 years). The most common gastrointestinal (GI) symptoms were bloating (47.8%), abdominal pain (47.1%) and diarrhea (30.7%), respectively. Also, 17 (12.1%) patients did not complain of any GI symptoms. 18 (12.8%) patients had aphthous stomatitis, 10.7% had dermatitis herpetiformis, 3.6% suffered from itching without a rash, two (1.4%) mentioned psoriasis and one (0.7%) had lichen planus. 19 (19.7%) of the female patients complained of menstrual bleeding disorders, 4% mentioned infertility, and 2% experienced primary amenorrhea. The most common comorbid condition was hypothyroidism in 16 (11.4%) patients. The most common endoscopic finding was duodenal scalloping (37.25%). In addition, 7.8% of the patients had a normal endoscopic appearance. 43 (30.7%) patients were classified as Marsh IIC, 25.7% Marsh IIIB, 17.8% Marsh IIIA, 12.8% Marsh II and 12.8% were classified as Marsh I.

Conclusion: Since celiac disease can present with non-GI manifestations and the majority of our patients had Marsh III classification, it seems that celiac disease must be considered as a routine screening test in GI clinics, and also, it should be kept in mind as a differential diagnosis in other specialty fields.

Keywords: Celiac, Epidemiology, Pathology, Endoscopy

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Introduction

Celiac disease is a chronic autoimmune disease of the small intestine, characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia. The disease is due to gluten sensitivity, a protein found in wheat and some other grains.¹ Although genetic predisposition is very important in its development, many other environmental factors contribute to its occurrence.^{2,3} In the classic form of celiac disease, the patient presents with malabsorption symptoms, including steatorrhea, weight loss, and signs related to nutrient and vitamin deficiencies. However, the disease also has atypical and silent forms.⁴ In the atypical

form, the patients have mild digestive symptoms, and they present with non-gastrointestinal (GI) symptoms, including neurological symptoms, anemia, tooth disorders, osteoporosis and/or infertility. In the silent form, the patients have no symptoms, and the disease can only be diagnosed via screening tests,⁵ but these patients face a greater risk as they develop digestive malignancies, especially intestinal lymphoma.^{3,6,7} Consequently, this disease is very important for various reasons, including its effects on the quality of life and life span of the patients.³

Many studies have so far been conducted on the prevalence of celiac disease in Iran. Based on a recent



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review and meta-analysis of 63 patients, the general prevalence of celiac disease in Iran was 3% based only on biochemical tests and 2% when the biochemical findings were histologically confirmed.⁸ In the study region (Mazandaran province), a study by Fakheri et al in 2004 on 1438 residents of Sari county reported that the prevalence of celiac disease in this population was 1%.⁹

However, the research performed in Iran has mainly dealt with the prevalence of this disease in various parts of the country, and few studies have investigated the frequency of its clinical manifestations and its relationship with the demographic characteristics of the patients. In a study conducted in Mashhad in 2014, celiac disease was more prevalent in female patients, and its initial demonstration was mostly accompanied by non-GI symptoms, and diarrhea was not a dominant symptom.¹⁰ Contrary to the research in Mashhad, diarrhea was the most prevalent symptom among the patients when they visited the clinic in another study that was carried out in southern Iran (Ahvaz).¹¹

In our geographic region (Mazandaran province, situated in the littoral of the Caspian Sea), no research has been conducted on clinical manifestations of celiac disease. Meta-analyses have shown that the risk of celiac disease and their presentations not only vary among different countries but also vary within countries. Therefore, the present study intended to determine the demographic, clinical, endoscopic, and pathological features of patients with celiac disease in Mazandaran province. Of course, the results of this research can help in determining the groups at risk of celiac disease and in earlier diagnosis.

Materials and Methods

In this descriptive research, all the patients with celiac disease referred by adult and pediatric GI specialists in Sari and the other Counties in Mazandaran province to the National Center for Registration of Celiac Disease at the Mostafavian Clinic of Imam Khomeini Hospital in Sari during 2018-2021 were studied with respect to demographic features, clinical symptoms, serological and pathological findings of duodenal biopsies and endoscopic findings.

To this end, the patients visiting this clinic were interviewed in person, and their laboratory, endoscopic, and pathological records were examined, and the information was recorded in the questionnaires designed for this purpose.

The exclusion criteria included the unwillingness of the patients to disclose this information and the incompleteness of the records that had confirmed the celiac diagnosis. Accordingly, histological findings from the duodenal biopsy based on the Marsh classification indicating the presence of celiac disease were needed in addition to positive serologic testing (presence of one of the IgA and/or IgG anti-glutadin, anti-endomysial, or anti-tissue transglutaminase antibodies) for the diagnosis of celiac disease. The only exception was the patients with

celiac disease who had dermatitis herpetiformis together with high titers of the antibodies associated with celiac disease and hence did not need intestinal biopsy.

Finally, the information obtained from the patients was analyzed by SPSS software (version 16) and using descriptive statistical tests (determination of frequency and mean) and the chi-square test.

Results

Based on the results, 140 patients were entered into the research, of whom 44 (31.4%) were male, and 96 (68.6%) were female. The mean age of the patients at diagnosis was 27.13 ± 13.4 years. The mean age of the female patients was 30.4 ± 12.3 years, and the mean age of the male patients was 20.06 ± 13.2 years. This indicated that there was a statistically significant difference in mean age between the female and male participants ($P < 0.05$). The youngest and oldest patients at diagnosis were aged 2 and 60 years. 12 (8.6%) patients said they had a history of celiac disease in their first-degree relatives. The mean body mass index (BMI) values of the patients was 22.37 kg/m^2 (41.4%, 21.4%, and 26.4% of the patients had normal, lower than normal, and higher than normal BMI values, respectively). As for the type of nutrition when they were infants, 71.4% received only breast milk, 10.7% received only infant formula, and 5.7% had both breast milk and infant formula.

Regarding GI symptoms at diagnosis, 17 (12.1%) patients did not exhibit any GI symptoms, 43 (30.7%) complained of diarrhea at the time of diagnosis, 32 (22.8%) mentioned constipation, 67 (47.8%) patients complained of bloating along with changes in bowel movements, 66 (47.1%) patients felt abdominal pain besides other GI symptoms and three patients only experienced nausea when they visited the GI clinic. However, 31 (22.1%) patients suffered from nausea along with other GI symptoms, including diarrhea and bloating. 26 (18.5%) patients suffered from weight loss at the time of diagnosis, and 19 (13.5%) patients mentioned gastroesophageal reflux together with the other GI symptoms. It must be mentioned that as some of the patients presented with a number of GI symptoms, the overall frequency of the above symptoms exceeded 100%. Table 1 presents the frequencies of the GI symptoms.

Also, significant numbers of patients had concomitant non-gastrointestinal symptoms at the time of diagnosis,

Table 1. The frequencies of gastrointestinal symptoms at the time of diagnosis

Clinical presentations		No. (%)
Gastrointestinal	Diarrhea	43 (30.7)
	Constipation	32 (22.8)
	Bloating	67 (47.8)
	Abdominal pain	66 (47.1)
	Weight loss	26 (18.5)
	Gastroesophageal reflux	19 (13.5)
	No gastrointestinal symptoms	17 (12.1)

including rheumatologic, mucocutaneous, neurologic, gynecological, and renal problems (Table 2).

The most common non-GI symptoms were peripheral neuropathy, muscle weakness, headache, abnormal uterine bleeding, and aphthous stomatitis.

Also, based on the results of the present research, a number of diseases were accompanied by celiac disease. The most prevalent concomitant diseases were hypothyroidism in 16 (11.4%) patients, diabetes in 14 (10%), rheumatoid arthritis in 4 (3.5%) patients, hyperthyroidism in 2 (1.4%), Down syndrome in 3 (1.2%), and lymphoma in 1 (0.7%) patient. Among the above-mentioned diseases, two patients had concomitant diabetes and hypothyroidism accompanying celiac disease, two suffered from concomitant rheumatoid arthritis and hypothyroidism that accompanied celiac disease, and one experienced diabetes together with hypothyroidism and Down syndrome accompanying celiac disease.

Regarding laboratory tests, 42.3% of the patients had anemia (31.5% microcytic hypochromic anemia and 68.5% normocytic normochromic anemia). In addition, the levels of aminotransferase levels were normal in 77.3% of the patients, but they were 2-3 times higher than the normal level in 18% of the patients, 3-5 times higher than the normal level in 1.8% of the patients and more than five times higher than the normal level in 1.8% of the patients.

Also, regarding endoscopic examination, the most

common findings were duodenal scalloping in 38 (37.25%) patients, duodenal atrophy in 15 (14.5%), hiatal hernia in 14 (13.7%), bulbar erosions in 11 (10.7%), gastric erythema in 11 (10.7%), bulbar nodularity in 1 (0.9%), duodenal ulcer in 2 (1.9%), evidence of gastroesophageal reflux in 7 (4.9%), duodenal erythema in 4 (3.6%) and gastric ulcer in 3 (2.9%) patients. In addition, 8 (7.8%) of the patients had a normal endoscopic appearance. Unfortunately, endoscopy reports of 38 patients were not available (Figure 1).

Moreover, based on the Marsh classification, the pathological findings were as follows: 43 (30.7%) patients were classified as Marsh IIIC, 36 (25.7%) as Marsh IIIB, 25 (17.8%) had Marsh IIIA, 18 (12.8%) had Marsh II and 18 (12.8%) were classified as Marsh I. It must be mentioned that no relationship was found between the severity of pathological involvement and the endoscopic findings or between the severity of pathological involvement and the clinical symptoms in the patients.

Discussion

This research was conducted on 140 patients with celiac disease who visited the Celiac Clinic of Mazandaran University of Medical Sciences whose demographic, clinical, endoscopic, and pathological features were investigated.

Most patients (68.8%) were women. This sex ratio is in concordance with the reports from others (79, 80). This may be somewhat due to the fact that women use healthcare services more frequently compared with men, and therefore, more female patients are diagnosed with celiac disease than men.^{12,13}

The mean age of the patients at diagnosis was 27.13 years. However, the mean age among the female patients was 10 years older, and the oldest age at recognition was 60 years. Recent research indicates a rise in the age at which celiac disease becomes symptomatic and diagnosed. A study performed in Italy showed that 15% of the patients recently diagnosed with celiac disease were more than 60 years old.¹⁴ Also, in another study from Finland, 2% of the patients with celiac disease were diagnosed between 52-74 years of age.¹⁵

Seventy-one percent of the patients in the present

Table 2. The frequencies of non-gastrointestinal problems at the time of diagnosis

Clinical presentations	No. (%)	
Rheumatologic	Arthritis	5 (3.6)
	Arthralgia	9 (6.4)
	Muscle cramps	12 (8.6)
	Bone pain	13 (9.2)
	Muscle weakness	32 (22.8)
Mucocutaneous*	Aphthous stomatitis	18 (12.8)
	Dermatitis herpetiformis	15 (10.7)
	Itching	5 (3.6)
	Psoriasis	2 (1.4)
	Non-specific dermatitis	2 (1.4)
	Hair loss	3 (1.2)
	Lichen planus	1 (0.7)
Neurologic	Headache	23 (16.4)
	Ataxia	1 (0.7)
	Seizures	5 (3.5)
	Peripheral neuropathy	34 (24.2)
	Depression	9 (6.4)
Gynecological (only among females)	Abnormal uterine bleeding	19 (19.7)
	Infertility	4 (4)
	Primary amenorrhea	2 (2)
Renal	Stone	5 (3.6)
	Proteinuria	1 (0.7)

*Dermatologic diseases were diagnosed and confirmed by dermatologists.

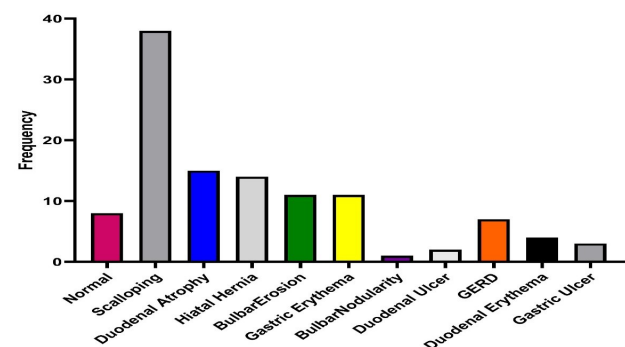


Figure 1. The frequencies of endoscopic findings in the patients with celiac disease

research were breastfed during their first two years of life. In the past, it was believed that long-term breastfeeding of children might reduce their chances of developing celiac disease in the future. This opinion was formed during the 1980s and 1990s when the incidence of celiac disease rose sharply in Sweden, where newborns received more food or infant formula and less breast milk.¹⁶ However, later large-scale research projects did not support this idea.^{17,18}

Regarding clinical symptoms, although celiac disease is mainly considered an intestinal disease, 12% of the patients did not exhibit any GI symptoms. Among the patients whose primary manifestations of the disease were the GI symptoms, bloating was the most common complaint (47.8%) followed by abdominal pain (47.1%), diarrhea (30.7%), constipation (22.8%) and nausea (22.1%). Of course, most patients presented with many simultaneous symptoms, and therefore, the overall percentage of the symptoms exceeded 100%. Recent studies indicate an increasing shift from GI symptoms to atypical symptoms in patients with celiac disease so that many adults diagnosed with this disease rarely complain of obvious diarrhea and/or metabolic disorders or malnutrition.^{19,20} This points out the need for paying attention to the atypical symptoms of celiac disease when patients visit GI clinics.

The most frequent non-GI symptoms were peripheral neuropathy in 24.2% of the patients, muscle weakness in 22.8%, menstrual disorders in 19.7% of the female patients, headache in 14.4%, and aphthous stomatitis in 12.8% of the patients. Of course, aphthous stomatitis can be considered among the GI symptoms, but it was put among the cutaneous-mucosal symptoms of celiac disease in the present research. The frequency of these symptoms also emphasizes that it is necessary to pay attention to the atypical symptoms of this disease.

Based on previous research, there is a close relationship between celiac disease and its neurological manifestations. In a study by Chin et al on the neurological manifestations of celiac disease, peripheral neuropathy was reported in 50% of the patients, and this symptom was, in some cases, observed even before the other manifestations of celiac disease.²¹ The cause of this neuropathy can be a deficiency of vitamins B2, B3, B6, and B12. The other important neurological manifestations of celiac disease are depression and seizures.^{22,23} In the present research, 6.4% of the patients with celiac disease who were diagnosed with depression received psychiatric treatment, and 3.5% of the patients with celiac disease had a history of seizures. The causes of these symptoms in patients with celiac disease are not very clear.

In our study, rheumatologic manifestations included muscle weakness in 22.8% of the patients, bone pain in 9.2%, and arthralgia in 6.4% of the patients. In addition, 3.6% of the patients had arthritis when they were diagnosed with this disease, which is because they simultaneously suffered from rheumatoid arthritis. Although celiac disease is accompanied by rheumatologic

manifestations, especially rheumatoid arthritis, it is not clear yet whether there is a causal relationship between these two diseases.^{24,25}

In 2019, Abenavoli et al conducted a review study on the cutaneous manifestations of celiac disease. Based on the results of this research, including more than 7000 articles, a strong relationship was found between celiac disease and only dermatitis herpetiformis or psoriasis. Other reported cutaneous manifestations were not based on the results of randomized clinical trials and were mainly according to case reports. These manifestations included urticaria, aphthous stomatitis, rosacea, cutaneous malignancies, and vitiligo.²⁶ Based on the results of our research, the most common cutaneous-mucosal manifestations accompanying celiac disease were aphthous stomatitis followed by dermatitis herpetiformis, itching without a rash, and psoriasis. As for the pathogenesis of these symptoms, it seems that improper function of the small intestine acting as a barrier prevented entry of antigens, caused special antigens to enter the body, and stimulated immunological responses involved in the appearance of cutaneous manifestations in patients with celiac disease.²⁷

Based on the results of the present research, concomitant diseases accompanying celiac disease were hypothyroidism, followed by diabetes, rheumatoid arthritis, and Down syndrome. Previous research indicated that patients with celiac disease faced a greater risk of developing autoimmune thyroid diseases, including hypothyroidism. In addition, a very close relationship was observed between celiac disease and type 1 diabetes and autoimmune polyglandular syndrome type 3.²⁸ These findings are in concordance with the results of the present research.

Furthermore, based on the results of previous studies, the risk of developing celiac disease in patients with Down syndrome is 20 times greater compared to the healthy population.²⁹ In our research, also, Down syndrome was the fourth most common condition associated with celiac disease, and three (2.1%) of the patients had Down syndrome. It should also be mentioned that the two above-mentioned patients with primary amenorrhea had Down syndrome. Therefore, the pathogenesis of amenorrhea might have been related to this genetic syndrome, not celiac disease itself.

According to the laboratory findings in the present study, 42.3% of the patients had anemia when they first visited the Celiac Clinic (31.5% had iron deficiency anemia and 68.5% normocytic normochromic anemia). Unfortunately, we did not have any information on folate and vitamin B12 levels in these patients to make a good interpretation of anemia in patients with celiac disease.

Based on research carried out by Martín-Masot et al on anemia in patients with celiac disease, anemia was a multifactorial complication in these patients. But in most cases, it was caused by iron, folic acid and/or vitamin B12 malabsorption, and also, in some cases, it was caused by GI bleeding resulting from the diseases, including

inflammatory bowel diseases associated with celiac diseases.³⁰

Another important finding in the present research was that 22.7% of the patients with celiac disease had higher than normal levels of aminotransferases. In a study by Castillo et al in 2015, about 40% of the 463 patients with celiac disease had elevated levels of transferases, but in most patients, the levels of aminotransferases returned to normal soon after they started a gluten-free diet.³¹ However, the related pathogenesis is not completely clear yet.

In the present study, the most frequent endoscopic finding was scalloping of the duodenal mucosal folds (37.2% of the patients). The other frequent endoscopic appearances of duodenal mucosa were atrophy of duodenal folds in 15 patients (14.5%), bulbar erosions in 11 (10.7%), and gastric erythema in 11 (10.7%) patients. Although celiac disease can have various endoscopic appearances, the endoscopic sensitivity for the diagnosis of this disease varies from 59% to 94%, and the specificity of these appearances for celiac disease is in the range of 92%-100%. In fact, these endoscopic findings may also be observed in other conditions, including giardiasis, autoimmune enteropathy, and HIV infection.³² Therefore, in addition to endoscopic appearance, histological findings play an important role in diagnosing celiac disease.

In our study, histologic evaluation showed that more than 86% of the patients were in advanced stages of Marsh classification (Marsh II or III), with Marsh III being the dominant type. This finding may indicate delays in the diagnosis of celiac disease, caused by both the physicians and the patients for delay in seeking medical visits. Although Marsh II and III are not sufficient for making a definitive diagnosis of celiac disease, they considerably help in its diagnosis.³³ It is noteworthy that, in the present study, no significant relationship was found between the endoscopic findings and the extent of the histologic involvement. This lack of a relationship has also been reported in other studies.³⁴

The present study has some limitations. First of all, most of our patients had been diagnosed with celiac disease many years ago, and therefore, they probably would make mistakes in remembering their initial symptoms. Another limitation resulting from this gap was that a percentage of the patients had lost the results of their endoscopic examination performed at the beginning of the diagnosis. However, the strong point of our study is that it is the first research on epidemiological, clinical, endoscopic, and pathological features of celiac disease in the southern littoral area of the Caspian Sea.

In conclusion, the estimated prevalence of celiac disease in the north of Iran is 1%.³⁵ Celiac disease can have atypical GI or even non-GI manifestations, and also, regarding the advanced stages of Marsh classification in most of our patients, it seems that the screening tests for celiac disease must be included in the routine screening strategies of GI clinics and also, be taken into account in other subspecialty clinics such as rheumatology, dermatology,

neurology, gynecology, and psychiatry.

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Competing Interests

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

Ethical Approval

This project was approved by the Ethical Committee of Mazandaran University of Medical Sciences.

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