Original Research Article

CELIAC DISEASE AMONG GASTROINTESTINAL PATIENTS IN YEMEN: ITS PREVALENCE IN GASTROINTESTINAL PATIENTS, SYMPTOMS AND ACCOMPANYING SIGNS; AND ITS PREVALENCE AMONG DIFFERENT AGES AND SEXES

ABSTRACT

Background and objectives: Coeliac disease, or celiac disease, is a long-term autoimmune disorder that primarily affects the small intestine. Classic symptoms include digestive problems such as chronic diarrhea, flatulence, malabsorption, loss of appetite, and failure of children to grow normally. The prevalence of celiac disease has not been established in Yemen, either in the general population or in symptomatic patients. Therefore, the current study aimed to assess the prevalence of disease in symptomatic patients and to investigate associated symptoms and signs; and whether prevalence of CD varies greatly between different ages and genders. **Methods:** A retrospective study based on the results of serological markers; IgA anti-tissue glutaminase and small bowel biopsies of 600 patients with gastrointestinal symptoms. Age, gender, clinical symptoms and co-morbidities were also considered and analyzed. Data were collected from hospital records during the period from March 2014 to December 2018. 600 suspected patients (245 males and 355 females) were subjects and the mean age of ± SD patients was 30.6 ± 14.5 years (range 2-92 years). **Results:** The prevalence of celiac disease among patients with gastrointestinal symptoms was 9.2%, . There was a significant association between CD with females (rate being 11.3% , odds ratio=1.9, p = 0.03), and 2-19 years age group (21.4% , odds ratio=4.3,p < 0.001), Considering the clinical signs and symptoms there was a significant association between celiac disease and chronic diarrhea (odds ratio = 18.4 times), steatorrhea (OR = 9.6), foul odor (odds ratio = 8.3 times), weight loss (Odds ratio = 5.7 times), anemia (odds ratio = 10.2 times), abdominal distension (odds ratio = 3.1 times), mouth ulcers (odds ratio = 7.2 times), abdominal bleeding (odds ratio = 13.5 times), diabetes mellitus I (odds ratio = 18 times), and hypothyroidism (odds ratio = 79.3 times). **Conclusion:** A high rate of celiac disease was identified among gastrointestinal symptoms patients arriving at the general hospital in Sana'a, Yemen, and this demonstrates the importance of general practitioners in identifying patients with celiac disease, especially in the absence of a medical facility for celiac disease, and this was facilitated through the EmA test. Our findings also indicate that celiac disease is more common in females, children and younger people, and there was an association between Celiac disease and the classic symptoms of this disease mentioned in the medical literature.

Key words: Celiac disease, signs, symptoms, prevalence, Yemen

INTRODUCTION

Celiac disease or Coeliac disease, is a continuing autoimmune illness that mainly involves the small intestine. Classic symptoms comprise digestive problems for instance chronic diarrhea, flatulence, malabsorption, loss of appetite, and failure of children to grow normally. This regularly begins between six months and two years of age. Non-classical symptoms are more frequent, in particular in people older than 2 years. There may be moderate or absent gastrointestinal symptoms, a large number of symptoms relating any part of the body, or no apparent symptoms. Celiac disease was first illustrated in childhood; nevertheless, it may arise at all ages. It is linked with autoimmune diseases, for instance type 1 diabetes and Hashimoto's thyroiditis [1]. Celiac disease results from a reaction with gluten, which is a group of different proteins found in wheat and other grains such as barley and rye. Moderate amounts of oats, free from pollution with further gluten-containing grains, are regularly tolerated[2]. The incidence of harms may depend on the type of oats. Celiac disease appears in people with a genetic predisposition. Upon exposure to gluten, the abnormal immune response may result in the production of many different autoantibodies that can involve a number of distinct organs. In the small intestine, this causes an inflammatory reaction and may lead to villous atrophy. This affects the absorption of nutrients, often leading to anemia[3]. The gold standards in diagnosing celiac disease are bowel biopsy and positive serological markers (anti-tissue IgA (Ttg IgA) antibody and anti-endomysial)[1]. HLA class II DQ2 and DQ8 haplotypes are found in nearly all patients with a sensitivity of nearly 100% and also in 30% to

40% of the population. On the basis of a very high negative predictive value, HLA typing can assist and support the exclusion of the diagnosis of celiac diseases in ambiguous cases in which the patient not have HLA-DQ2 and DQ8[4]. On the other hand, making the diagnosis is not continuously simple[5]. Often, serum autoantibodies are negative, [4] and many people have only minor changes in the intestine with normal villi. People may have severe symptoms and may be explored for years before a diagnosis is made[7]. Currently, the diagnosis is increasingly being made in people who have no symptoms as a result of screening. However, the evidence regarding the effects of screening is not sufficient to determine its usefulness. While this disease is caused by a persistent intolerance to gluten proteins, [3] it differs from wheat allergy which is known to be very rare.

Epidemiologically, celiac disease affects about 1 in 100 to 1 in 300 of the world's population[1]. This rate may be increased among those at risk; Like first-degree relatives: 1 in 10, or like second-degree relatives: 1 in 39 and 1 in 56 in asymptomatic patients [1]. Moreover, the prevalence of celiac disease among unexplained iron deficiency anemia's is 3% to 15%, 2% to 15% among type 1 diabetes, 2% to 7% among hypothyroidism, 3% to 6% among Addison's disease , and autoimmune hepatitis, 3% among irritable bowel syndrome, ataxia, and idiopathic neuropathy[1]. Studies in gastroenterology and/or autoimmune diseases are still limited in Yemen and only a few studies have been conducted on autoimmune hepatitis [9,10], and the relationship between CD and infertility by measuring sex hormones in CD compared to controls healthy [11], anti-mannose auto-antibodies in patients with rheumatoid arthritis [12], and intestinal infection among adults and children[13-15]. The prevalence of celiac disease has not been established in Yemen, either in the general population or in symptomatic patients. Therefore, the current study aimed to assess the prevalence of disease in symptomatic patients and to investigate associated symptoms and signs; and whether prevalence of CD varies greatly between different ages and genders.

MATERIALS AND METHODS

STUDY DESIGN AND SETTING

This retrospective study was conducted at the University of Science and Technology Hospital (USTH) in Sana'a, Yemen. USTH is one of the main hospitals in Yemen, which receives patients from all over the country and also the city of Sana'a is the capital of Yemen. For these factors, the results of this study may represent the whole country.

DATA COLLECTION

600 symptomatic patients were enrolled in this study. Among them, 245 (40.8%) males and 355 (59.2%) females attended pediatric clinics, internal medicine clinics, and gastroenterology units for medical care in USTH from March 2014 to December 2018. Data were obtained from electronic patient records after approval of the hospital ethics committee. By enzyme-linked immunosorbent assay (ELISA), positive ATtg IgA criteria greater than 10 times the ULN in children or less than 10 times the ULN but confirmed by small bowel biopsy, were the criteria used to measure the prevalence of celiac disease. Hemoglobin levels (to define anemia based on a hemoglobin concentration less than 11 g/dL) were also included. The subjects were divided into categories based on gender and age. Clinical signs, symptoms and other diseases associated with celiac disease were also collected and analyzed.

DATA ANALYSIS

The whole data were analyzed by IBM SPSS Statistics 22.Ink (International Business Machines Corporation, New York, USA). The outcomes for variables were given in the form of rates (%). Chi Square was used for categorical variables that measured association among categorical variables. *P*-values less than 0.05 were considered significant. Odds of celiac disease (odds ratio, OR) were also analyzed by sex, age groups, symptoms, signs and other syndromes, with 95% *CI*, X^2 and *p* to test for significance of association with the above factors.

RESULTS

Table 1 shows the age and gender distribution of patients with gastrointestinal symptoms admitted to the University of Science and Technology Hospital, Sana'a, Yemen - during the period from March 2014 to December 2018 who underwent examination for serological markers; Anti-tissue IgA glutaminase and small intestine biopsies for celiac disease. The percentage of females was 59.2% compared to 40.8% for males. Looking at the age groups, most patients were in the age group 20-40 years (58.2%), followed by 2-19 years (21%) and 41-60 years (18%), while the >60 years group was

only 2.8%. Table 2 shows the prevalence of serological markers. Anti-tissue IgA glutaminase and small bowel biopsies for celiac disease among different sex and age groups of patients with gastrointestinal symptoms. The prevalence of celiac disease among patients with gastrointestinal symptoms was 9.2%. Considering gender, there was a significant association between celiac disease and females with the rate being 11.3% with an odds ratio equal to 1.9, CI equal to 1.1–3.9 (p = 0.03). Considering ages, there was a significant association between celiac disease with 2-19 years as the rate was 21.4% with an odds ratio equal to 4.3, CI equal to 2.4-7.6 (p < 0.001), while there was no association between celiac disease and age groups other. Considering the clinical signs and symptoms associated with intestinal symptoms compared to celiac disease (Table 3), there was a significant association between celiac disease and chronic diarrhea (odds ratio = 18.4 times), steatorrhea (OR = 9.6), foul odor (odds ratio = 8.3 times), weight loss (Odds ratio = 5.7 times), anemia (odds ratio = 10.2 times), abdominal distension (odds ratio = 3.1 times), mouth ulcers (odds ratio = 7.2 times), abdominal bleeding (odds ratio = 13.5 times), diabetes mellitus I (odds ratio = 18 times), and hypothyroidism (odds ratio = 79.3 times).

DISCUSSION

Celiac disease is an immune condition mediated by systemic disease of the small intestine Symptoms related to malabsorption and/or activation of immunity and autoantibodies to tissue transglutaminase (TTG). Celiac disease is distinctive amongst autoimmune diseases in that a generate, dietary gluten, has been recognized, and its removal resolves symptoms and enteropathy in the greater part of patients. Increased awareness and development of serological tests have led to an increased incidence of disease and a change in the distribution of clinical features[1] . In Yemen, its prevalence has not yet been estimated, and current work is an attempt to determine the rate of CD among clinically suspected patients. The prevalence of celiac disease among patients with gastrointestinal symptoms in the current study was 9.2%. Compared with our observations, the prevalence of CD in Yemen exceeds the rate of CD among suspected Finns 5.33% among patients with gastrointestinal symptoms[16] and other previous rates of disease as in Saudi Arabia, South Yorkshire, Amsterdam, the Netherlands and in North America are among the symptoms gastrointestinal representing; 7.6%, 4.7%, 3.0% and 2.0%, respectively[17-20]. On the other hand, results similar to ours were presented by Dickey *et al* and Hopper *et al* [21,22] where the incidence of celiac disease among patients with undiagnosed gastrointestinal symptoms was about 9%. In contrast to the average (9.2%), the prevalence of CD among Iranian patients with irritable bowel syndrome was about 12% and among patients with gastrointestinal symptoms in Italy was about 13% as reported by Shahbazkhani *et al* and Carroccio *et al* respectively [23,24]. Considering gender, there was a significant association between celiac disease and females with a rate of 11.3% (OR = 1.9 (CI = 1.1-3.9, p = 0.03) (Table 2). This result is similar to that reported where the incidence of celiac disease is higher in females than in males (17.0 versus 7.8 per 100,000 person-years) in pooled analysis[25] , but this may be because men are more likely to remain undiagnosed. A systematic review and meta-analysis found a slight increase in seropositivity among women participating in screening studies [26] although some studies in adults have found that men and women have the same seroprevalence rates[27,28]. Men are less likely to undergo duodenal biopsy during upper endoscopy for indications such as diarrhea and weight loss, which may contribute to underdiagnosis[29]. Celiac disease can develop at any age, including the elderly [30]. Considering age in the current study, there was a significant association between celiac disease and age group 2-19 years where the rate was 21.4% with an odds ratio equal to 4.3, CI equal to 2.4-7.6 (p < 0.001) (Table 2). This is similar to what has been previously reported where the incidence of CD was higher in the younger age group. This rise in CD at a young age can be explained by the fact that such diagnoses do not necessarily indicate the late detection of celiac disease long ago - it may result from a de novo loss of gluten tolerance. Studies of serial serum samples have reported loss of gluten tolerance in adulthood[31]. However, recent prospective cohort studies have found that most patients develop celiac disease before the age of 10 years[32,33]. Moreover, in our study, the prevalence of anemia was widespread (71.4%, OR = 40.4 times, P<0.001) (Table 3) among ATtg IgA-positive patients in agreement with several studies[34, 35]. These patients are more likely to have acute disease compared to non-anaemic CD patients according to Daya, *et al* [36].

Once serological testing began in the 1990s, there was an expansion of clinical offerings leading to a diagnosis of celiac disease. The proportion of patients with celiac disease who had diarrhea decreased from 73% before 1993 (the year in which serological testing became available at the study site) to 43% thereafter [37]. Although diarrhea continued to be the most common symptom at presentation, most patients received the diagnosis based on this on other signs or symptoms, such as osteoporosis, anemia, bloating, or irregular bowel habits; some had less common symptoms, including infertility[9], migraine headaches [38] neuropsychiatric symptoms[39] and abnormal liver enzyme levels[40].

In the current study considering the clinical signs and symptoms associated with intestinal symptoms compared to celiac disease, there was a significant association between celiac disease and chronic diarrhea (odds ratio = 18.4 times), steatorrhea (OR = 9.6), foul odor (odds ratio = 8.3 times), weight loss (Odds ratio = 5.7 times), anemia (odds ratio = 40.4 times), abdominal distension (odds ratio = 3.1 times), mouth ulcers (odds ratio = 7.2 times), abdominal bleeding (odds ratio = 13.5 times), diabetes mellitus I (odds ratio = 18 times), and hypothyroidism (odds ratio = 79.3 times). These signs and symptoms combined outnumber diarrhea, so diarrhea can no longer be referred to as typical and presentation without diarrhea as atypical. As such, a 2013 consensus statement renamed diarrhea and non-diarrhea presentations as classic and non-classical celiac disease, respectively[41]. Regardless of the type of symptoms, there is often a long-term delay between the onset of symptoms and a diagnosis of celiac disease. A national survey of patients with celiac disease in the US found the median duration of symptoms to be 11 years before diagnosis [42] and a UK study found the median duration to be 4.9 years[43]. In the current study, abnormal LFT occurred in 20% of CD patients, and this is lower than that performed by Castillo *et al.* as liver biochemical abnormalities were presented in 40% of patients newly diagnosed with celiac disease, according to Castillo *et al.* series the slight increases observed in aspartate and alanine transaminases are the most common abnormalities [40]. The incidence of celiac disease is increasing with its worldwide spread. There is a trend towards an increased diagnosis of non-classical presentations, and there is emerging evidence for accurate non-biopsy diagnosis in selected children[32]. Newly developed diagnostic tools, such as the HLA-DQ-based blood test - gluten tetramer, may change the way we diagnose celiac disease in the near upcoming, impending validation and scalability. This technique, combined with validation of serology-based diagnostic algorithms, may lead to a change in diagnostic criteria as a small bowel biopsy is no longer necessary while patients continue to follow a gluten-containing diet. These changes may transform the roles of gastroenterologists, from diagnosis to management and follow-up. If an evidence-based, biopsy-free strategy is developed for diagnosis, the incidence of celiac disease may increase further and stimulate interventional studies to prevent celiac disease in at-risk individuals [1].

CONCLUSIONS

The prevalence of CD among Yemeni patients with gastrointestinal disorders was as high as 9.2%, especially among children and adolescents. The disease was prevalent among females. On the other hand diagnosis by serological markers is useful in detecting CD in these patients. However, more studies are needed to support and confirm our findings and conclusions. According to this high prevalence, clinicians should pay more attention to CD when examining huge different symptoms especially among women, children and teens to avoid misdiagnosis or long-term delay diagnosis.

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AUTHORS' CONTRIBUTIONS

All authors contributed to the study design, analysis and manuscript writing.

ETHICAL APPROVAL

Ethical approval was obtained from the Ethics Committee from the USTH Sana'a, Yemen.

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Table 1: Age and gender distribution of patients with intestinal symptoms admitted to University of Science and Technology Hospital, Sana'a, Yemen - during the period from March 2014 to December 2018

Characters	Number	%	P
Gender			
Male	245	40.8	<0.05
Female	355	59.2	
Age groups			
2-19 years	126	21	<0.05
20-40 years	349	58.2	
41-60 years	108	18	
>60 years	17	2.8	
Total	600	100	Mean ±SD =30±14.5 years

*significance level less than 0.05 (P).

Table 2: Prevalence of Serological Markers; Anti-tissue IgA glutaminase and small bowel biopsies for celiac disease among different sex and age groups of patients with intestinal symptoms

Characters	celiac disease n=55		**OR**	**CI 95%**	**X2**	**p**
	No	%				
Gender						
Male n=245	15	6.1	0.5	0.2-0.9	4.6	0.03
Female n=355	40	11.3	1.9	1.1-3.6	4.6	0.03
Age groups						
2-19 years n=126	27	21.4	4.3	2.4-7.6	28.8	<0.001
20-40 years n=349	23	6.6	0.4	0.2-0.8	6.6	0.009
41-60 years n=108	5	4.6	0.4	0.16-1.1	3.2	0.07
>60 years n=17	0	0	00	0-1.9	1.7	0.18
Total n=600	55	9.2				

Table 3: Clinical signs and symptoms associated with intestinal symptoms compared to celiac disease patients admitted to University of Science and Technology hospitals, Sana'a, Yemen - during the period from March 2014 to December 2018

Symptoms and signs	Patients with intestinal symptoms **n=545**		**celiac disease n=55**		**OR**	***CI* 95%**	X^2	***p***
	No	%	%	No				
Chronic diarrhea	223	40.9	51	92.7	18.4	6.6-56	54	<0.001
Steatorrhoea	278	51	50	90.9	9.6	3.7-24.5	32	<0.001
Foul odor	191	35	45	81.8	8.3	4.1-16.9	45	<0.001
Weight loss	376	68.9	51	92.7	5.7	2-16.1	13.7	<0.001
Fatigue	321	58.9	39	70.9	1.7	0.9-3.1	3	0.08
Anemia	31	5.7	39	70.9	40.4	20.3-80.2	206	<0.001
Abdominal pain	447	82.2	49	89	1.8	0.7-4.2	1.7	0.18
Cramping	387	71	41	74.5	1.2	0.6-2.1	0.3	0.55
Abdominal distension	277	50.8	42	76.4	3.1	1.6-5.9	13	<0.001
Mouth ulcers	9	1.7	6	10.9	7.2	2.5-21	17.5	<0.001
Irritable bowel syndrome	169	31	3	5.5	0.12	0.03-0.4	15.9	<0.001
Abdominal bleeding	11	2.02	12	21.8	13.5	5.6-32.5	53.1	<0.001
Abnormal LFT	114	20.9	11	20	0.9	0.4-1.8	0.02	0.87
Diabetes mellitus I	3	0.55	5	9	18	4.1-77.8	27.6	<0.001
Hypothyroidism	1	0.18	7	12.7	79.3	9.5-658	59.7	<0.001