Celiac disease in South-West of Iran

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AIM: Celiac disease is characterized by life-long gluten intolerance. Clinical features of patients with celiac disease are variable. Studies about the prevalence of celiac disease in our country are scarce and there is no study on the prevalence of celiac disease in southern Iran. In the current study, clinical, laboratory and histological features of 52 patients with celiac disease were evaluated.

METHODS: In a cross-sectional study we retrospectively studied the characteristics of 52 celiac patients at Ahwaz JundiShapur University Hospitals (AJSUH) from November 1, 1999 to 1st Sep 2004. Intestinal biopsy and serum antigliadin and anti-endomysium antibodies were used for the diagnosis of patients. Mucosal lesions were classified according to the criteria of Marsh. Antigliadin antibodies were measured with a commercial enzyme-linked immunosorbent assay. Anti-endomysium antibodies were analyzed by indirect immunofluorescence with the use of a section of monkey esophagus. Routine hematological and biochemical analyses and measurement of immunoglobulin levels were undertaken.

RESULTS: Male: female ratio was 1.08. The mean ± SD patient age was 21 ± 4.5 years (range 10-70 years) and the most common symptoms were diarrhea and weight loss (78.8%) followed by fatigue (73.1%), palor (65.4%), anorexia (40.4%), abdominal distention (32.7%), and failure to thrive (23.1%). Diarrhea and weight loss and fatigue were the most common findings. Iron deficiency anemia was found in 63.2% of patients and this became the most common symptoms were diarrhea and weight loss (78.8%) followed by fatigue (73.1%), palor (65.4%), anorexia (40.4%), abdominal distention (32.7%), and failure to thrive (23.1%).

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy characterized by chronic inflammation of the small intestinal mucosa and the presence of typical auto antibodies. In epidemiological studies the prevalence has been found extremely variable[1]. The diagnosis can sometimes be difficult due to the wide spectrum of signs and symptoms. Environmental and genetic factors contribute to the clinical presentation of the disease[2,3]. Prevalence rates of 1:120 to 1:300 have been reported in Western Europe[4,5]. The clinical picture of the disease includes milder forms and older age at diagnosis[6]. Screening programs within populations indicate that the disease is undiagnosed[7]. Adult celiac patients tend to remain asymptomatic or oligosymptomatic. However, the increased risk of autoimmune diseases and intestinal lymphoma or carcinoma in individuals with CD calls for screening on the slightest suspicion and the disease needs to be treated even when there are no symptoms[9]. A previous report from Iran indicates an estimated prevalence of up to 1/166 for celiac disease[9]. To the best of our knowledge few data have been available about the epidemiological features of adult CD in west southern of Iran (Khuzestan).

The aim of this study was to investigate prospectively the clinical picture of diagnosed adult CD in this area.
MATERIALS AND METHODS

Study group
All newly diagnosed cases of CD were registered prospectively from November 1, 1999 to 1st Sep 2004 at Ahwaz JundiShapur University Hospitals (AJSUH). A celiac disease-specific questionnaire was used for data collection and asked for name, birth date and present height and weight, and sought information on intermittent abdominal pain, constipation, diarrhea, known chronic diseases and, associated disorders and family history of celiac disease. Physical examination, blood chemistry, urinalysis, and examination of stool for occult blood, ova and parasites were performed for all patients. If clinically indicated, other para clinical workups such as thyroid function tests, colonoscopy, small bowel study and abdominal ultrasonography were requested. Prior to the diagnostic procedures, informed consent was obtained from all the patients in the study.

CD serology
Total serum IgA level was measured in all subjects to identify IgA deficient cases. IgA antibody titres against gliadin were measured using a commercial enzyme-linked immunosorbent assay (Biosystem, Madrid, Spain). An IgA antibody against gliadin greater than 20 AU/mL was considered positive. Serum IgA antibodies against endomysium were also measured by immunofluorescence (Biosystem).

Diagnostic criteria
Patients who tested positive for IgA antibodies against gliadin or IgA antibodies against endomysium and cases with IgA deficiency underwent upper endoscopy (with Pentax EG2930K endoscopic equipment after an overnight fasting), and six biopsies were taken from the second portion of the duodenum. The biopsy samples were incubated in neutral buffered formalin and processed according to standard procedures. All biopsy specimens were reviewed by two pathologists experienced in celiac disease pathology and graded according to the modified Marsh classification (10:11).

Patients identified as having CD in biopsy specimens were started on a gluten-free diet. The patients were re-evaluated regularly by repeated IgA antibodies against endomysium serology and repeated upper endoscopy after 6 months. An excellent response was defined as complete elimination of all symptoms. Partial elimination or improvement in symptoms and hemoglobin levels during the follow up period there was a significant gain in weight and height of patients. Only 10% (5 cases) had their first-degree relatives screened for the disease and all of them were negative.

Our study protocol was approved by the ethics committee of the Ahwaz Jundishapur University of Medical Sciences.

Statistical analysis
Collected data were coded, analysed and computed, using the Statistical Package for Social Sciences (SPSS) version 10 (SPSS Inc., Chicago, IL, USA). Simple statistics such as frequency, and standard deviation were used. Chi-square and Student's t-tests were used for comparison.

DISCUSSION
We performed a prospective study on the newly diagnosed cases of CD in the south-West of Iran 1999-2004. There is a little clinical data available about celiac disease in this area where the disease is considered rare. This is due to lack of a registry system of celiac patients and awareness

RESULTS
A total of 52 patients were identified over the period of our study. Males numbered 27 and females 25 giving a male to female ratio of 1:08. The mean ± SD patient age was 21 ± 4.5 years (range 10-70 years). Twenty-two of these 52 were adults whereas the remainder were children (<15 years). Short stature and refractory anemia were the most common findings. The most common symptoms were diarrhea and weight loss (78.8%), followed by fatigue (73.1%), anorexia (40.4%), abdominal distention (32.7%), and failure to thrive (23.1%). Diarrhea and weight loss and fatigue were the most common findings. Anemia was found in 63.2% of patients and this became normal after adoption of a gluten-free diet in all patients (Figure 1).

Anemia was suggestive of iron deficiency in all cases with low serum iron levels and elevated total iron binding capacity. Immunoglobulin A, IgG antigliadin antibodies and IgA anti-endomysium antibodies were found in 33 and 48 cases, 78.8 and 85.4% of patients, respectively. Biopsy of the small intestine revealed that 90.4% of patients had typical lesions according to the Marsh classification. Skeletal radiographs were normal in all patients. Bone mineral densitometry showed osteoporosis in each of the 7 adult patients in which this test was performed (defined as Z score less than -2.0). Follow up data was available in 46 cases. The mean follow up period was 38 mo. During the follow up period there was a significant gain in weight and improvement in symptoms and hemoglobin levels in all the cases. Only 10% (5 cases) had their first-degree relatives screened for the disease and all of them were negative.
of this disease and a delay in physicians reaching the diagnosis of celiac disease. The primary aim of this study was to describe the clinical features at presentation in a group of Iranian patients diagnosed with celiac disease in Khouzestan in west southern of Iran.

The demographic characteristics of adult celiac patients in our area were similar to the clinical features described from populations in New Zealand[12], South Yorkshire[13] and Sweden[14] with a peak in diagnosis in the second decade of life[15]. Our study shows a female to male ratio of 1.08 a female predominance in keeping with published studies[10-13]. Twenty-two (42%) of biopsy-proven patients in our study had been diagnosed in childhood (< 15 years). More than 78.8% of patients in this survey presented with diarrhea. This frequency was higher than series of patients from Europe[19] or Canada[11]. Diarrhea with or without malabsorption syndrome is regarded as the classical presentation of celiac disease[18]. In countries where the disease is considered to be common, the percent of patients presenting with diarrhea has been declining. In a study from Edinburgh only 50% presented with diarrhea[20]. Other presentations have been termed atypical, silent, or sub clinical[18] and include anemia, bone disease vague GI symptoms, or hypertransaminasemia of unknown origin. The higher rate of patients with the typical or classical presentation in our study suggests decreased awareness of celiac disease and its various atypical presentations among physicians in the south-West of Iran. Many of celiac patients in our study have had a previous diagnosis of irritable bowel syndrome. It is not usual practice to screen these patients for celiac disease. However, this diagnostic group represents a large percentage of patients seen in a gastroenterology practice[24] and may in fact harbor a large number of undiagnosed celiac patients in our country. In a recent study by Shabazkhani et al one hundred and five cases of irritable bowel syndrome patients referred to a university clinic in Tehran, were tested for celiac disease. They found 12 (11.4%) cases with celiac specific antibodies (serum IgA antibodies against gliadin, IgG antibodies against gliadin and antibodies against endomysium), of which 11 (10%) proved to have celiac disease confirmed by duodenal biopsy. The authors suggested that all patients suffering from irritable bowel syndrome should be screened for celiac disease in Iran[21]. We have noted a long duration of symptoms before diagnosis (mean of 3.5 year in our study) this was mostly due to a delay in reaching the diagnosis of CD and a previous diagnosis of irritable bowel syndrome in our cases.

A plausible explanation would be that physicians regard adult celiac disease as rare and fail to consider it in clinical situations other than the classical chronic diarrhea and malabsorption.

A repeated duodenal biopsy to demonstrate improvement of villous atrophy on gluten free diet is advisable for confirmation of diagnosis in CD[22]. All the cases with CD in our study had a good response to GFD, thus obviating the need for a repeat biopsy to demonstrate improvement of duodenal villous atrophy. An association between celiac disease and autoimmune disorders, such as type I diabetes, autoimmune thyroid disease, and Sjögren’s syndrome, has been well documented in the literature[23].

We found a higher frequency of associated diseases (40.3%) than in most other studies (10%-15%)[23], that could be due to the increasing age at diagnosis (Table 1). In our study, the percentage of celiac patients who had a diagnosis of inflammatory bowel disease and thyroid disease were 15.3% and 11.6%, respectively, compared to estimates of 3%-5% and 3% reported in the literature[24]. Dermatitis herpetiformis and IgA deficiency are relatively common extraintestinal manifestations of celiac disease, but no patients were noted to have such extraintestinal manifestations in our cases. Our survey confirms the increased incidence of small bowel malignancies, adenocarcinoma, and EATCl, in celiac disease[25]. The malignancies of two cases (male) were lymphoma and occurred in the jejunum. The patients presented with bowel obstruction, and anemia. These two cases had a long history of symptoms of celiac since childhood. Adherence to a gluten-free diet reduces the risk of developing malignancies[26]. Therefore, earlier diagnosis may have prevented the development of malignancy. We don’t know how well the patients with lymphoma had adhered to the diet from the time of celiac diagnosis to the time of lymphoma diagnosis. About 8% of patients in our study were diagnosed with celiac disease at age 40. Men were more prominent in this group. These patients also had a long duration of symptoms. There was a trend toward more hip fractures in patients diagnosed at age 40 compared to those diagnosed at age < 40. Earlier diagnosis may prevent the development of osteoporosis and subsequent fractures[27]. There was a high frequency of metabolic bone disease and secondary hyperparathyroidism (up to 50%) in a cohort that was reported in untreated celiac disease cases from Turkey[28]. Prevalence of metabolic bone disease in Iranian patients with CD is not known. Bone mineral densitometry showed osteoporosis in each of the7 adult patients in which this test was performed (defined as Z score less than -2.0). These data underscore the need for adding calcium and vitamin D supplementation to gluten free diet even though they may be asymptomatic or show no biochemical or radiological evidence of bone disease. In summary, our study provides data about the clinical features of celiac disease in our area in south-West of Iran. The majority of patients who presented with diarrhea had a long duration of symptoms before diagnosis and we considered the diagnosis delayed. Celiac disease may not always present with classical clinical features so the possibility of this disease should be kept in mind. Celiac disease may result in a markedly increased risk for the development of small bowel malignancies and earlier diagnosis is very important. With the widespread

| Disorders                          | (%) | %    |
|-----------------------------------|-----|------|
| Inflammatory bowel disease        | 8   | 15.3 |
| Thyroid disease                   | 6   | 11.6 |
| Diabetes mellitus type 1          | 4   | 7.7  |
| Collagen vascular disease         | 3   | 5.7  |
| Total                             | 21  | 40.3 |

Table 1 Frequency (%) of associated disorders in study group
availability of screening tests for celiac disease, identifying cases in at risk groups by screening should also be considered.

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