Common Clinical Symptoms and Concomitant Disease in Celiac Patients – A Large Cohort Study in the North-East of Iran

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Abstract

Objectives: This study aimed to provide an overview of large cohort focusing in different clinical symptoms and concomitant disease in CD patients.

Methods: Out of total 1,164 cases, 78.86% of cases were adults, mean age 29.67 ± 15.94 and sex ratio (f/m) was 2.40. Evaluated clinical characteristics included BMI, Marsh, TGA-IgA titer, main symptoms and concomitant disease.

Result: 96.86% of CD cases were seropositive and more than 88% of patients had villous atrophy that 48.89% of them were type c. Dyspepsia 35.23%, diarrhea 18.52%, were main CD clinical symptoms. The common concomitant diseases were including nervous problems 57.43%, anemia 54.25%, osteopenia 28.23% and skin disease 23.54%.

Conclusion: The classic type is common type of CD in northeast Iran. Dyspepsia and diarrhea main clinical symptoms in these patients, consequently we recommended to screening for CD in cases whiteout classic symptoms (such as dyspepsia). Also recommended to screening for concomitant disease such as nervous problems, bone disease and anemia in female CD patients in first visit.

Keywords: Celiac disease, concomitant disease, main clinical symptoms

Introduction

Celiac disease is an autoimmune disorder characterized by mucosal injury in response to gluten in genetically predisposed individuals. CD accounts for about 1% of the population worldwide and is rapidly increasing because of availability of serologic tests which have high sensitivity and specificity.

The clinical manifestations of CD can vary from asymptomatic CD to classic or typical intestinal symptoms such as diarrhea, weight loss, and abdominal pain and atypical or non-classical symptoms including iron deficiency, bloating, constipation, chronic fatigue, headache, osteoporosis, neurologic disorders (e.g., depression and gluten ataxia), reproductive disorders (e.g., menarche disorders and menopausal disorders), and oral/cutaneous disorders (e.g., dermatitis herpetiform). By knowing wide variety of clinical presentation, early diagnosis and treatment of CD by gluten free diet (GFD) is important in patient out come and long term complications of disease. The prevalence of autoimmune diseases and malignancies has been reported to be higher in CD patients and even in their first-degree relatives. These patients are at risk of long-term complications, such as gastrointestinal and extra-intestinal malignancies and autoimmune disorders. Up to 30% of concomitant immune-mediated diseases have been reported in CD patients compared to (3–11.6%) in the general population. Moreover, CD has been described as a risk factor for enteropathy-associated T-cell lymphoma (EATL), non-Hodgkin lymphoma, and gastrointestinal tumors and a protective factor for other types of malignancies such as breast and lung cancers. The etiology of this disease is multifactorial, including environmental (gluten and intestinal infections), genetic, and immunological factors with a high genetic susceptibility, proposed by studies on HLA-DQ2 and HLA-DQ8 haplotype associations with CD. A significant proportion of CD patients are diagnosed through screening at-risk populations such as family members of patients with CD and insulin-dependent diabetics, but mostly remain undiagnosed.

A combination of serology testing and duodenal biopsy (increase intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy) is required to diagnose CD in adults. Currently, the only approved treatment for CD patients is a strict GFD. Improvement and resolution of symptoms occur after days or weeks after a GFD is implemented and often leads to normalization of serological markers and duodenal villous atrophy.

There are studies about risk factor, clinical finding and presentation and association of CD with other disorders in cohorts all over the world. Despite the high prevalence of CD in Iran due to the high rate of gluten and bread consumption, no previous well-designed cohort study was conducted in this region. Therefore, establishing the demographic characteristics and different clinical manifestations of this disease may provide important information regarding its timely diagnosis and proper management.

To the best of our knowledge, this is the first large cohort study of CD patients done in the Northeastern Iranian province of Khorasan Razavi, extensively exploring the clinical manifestations and co-occurrence of immune-mediated diseases in these patients.
Methods

Study Setting & Design

This retrospective study includes a cohort of celiac patients registered in the Celiac Disease Center of Mashhad University of Medical Sciences (MUMS), located in the northeastern Iran. This cohort was comprised of the records of all patients (with signs or symptoms of celiac) that were referred for diagnosis to the Celiac Disease Center from Khorasan and other neighboring provinces between 2010 and 2020. The data was analyzed using STATA version 12 (STATA, USA, 2009). The level of significance was less than 0.05 for all statistical tests. This study has been approved by the ethics committee of Mashhad University of Medical Sciences (Code: IRMUMSREC.1396.112). Furthermore, a written informed consent has been obtained from all participants.

Study Population

Study population was a cohort of 1164 patients with definite or clinical diagnosis of Celiac Disease. Diagnosis of CD was ascertained by positive celiac serology (TGA-IgA) and Marsh ≥ 2 histology on duodenal biopsy. TGA-IgA were assessed by enzyme-linked immunosorbent assay, Kit (Euro immune, Germany) in a research laboratory. Biopsy reports based on Marsh and modified Marsh Oberhuber Classification. Seronegative CD cases was diagnosed based on mucosal atrophy and HLA typing or challenge test after ruling out all other cause of mucosal atrophy including Crohn’s, infection, radiation, HIV, CVID, malignancy and peptic deodenitis and drug use. IgA deficiency patients were diagnosed based on pathology and IgG base serology of TGA and anti DGP. Seropositive CD cases were included in this cohort without biopsy, if had raised TGA-IgA and response to GFD and compatible HLA and typical presentation. Also patients without villous atrophy were included, if they were symptomatic and had high serology titer more than 10 times of normal and compatible HLA.

Data Collection

Clinical and demographic variables were included age, gender, height, weight, symptoms, Type of diseases (seropositive, seronegative or others), thyroid function, liver function and immune mediated diseases and other concomitant diseases such as Skin problem and Nervous problem were extracted from the database. Main symptoms that assessed in these patients were including dyspepsia, diarrhea, weight loss, flatulence, reflux, abdominal pain and others symptoms. TGA-IgA levels were reported in unit per milliliter using the manufacturer’s supplied reference ranges: 0–20 negative, >20 positive. The highest standard in the assay was >200, (10 times upper limit of normal).

Results

Characteristics of the Patients

Of the total of 1,164 cases, 78.86% of cases were adults (age 14 or older). 70.64% were female (n = 811) and sex ratio was (F/M) 2.40. The mean age at the time of the first visit was 29.67 ± 15.94 years (ranging from 1 to 76 years) and mean age not different between genders (male = 28.99, female = 29.95, P = 0.35). However 23.63% of patients (age >15 years old) had lower weight, but 48.49% of them had normal BMI (n = 353) (Table 1), and fortunately only 3.88% of this cohort were smoker (n = 32).

| Table 1. Baseline characteristics of celiac patients |
|----------------------------------------------------|
| **Variables**                                      | **Total** | **Gender/female** | **Sig** |
| BMI (age >15 years)                                |           |                  |        |
| <19                                                | 172 (23.63)| 122 (70.93)       | P = 0.10a |
| 19–25                                              | 353 (48.49)| 249 (70.54)       |        |
| 25–30                                              | 147 (20.19)| 98 (66.67)        |        |
| >30                                                | 56 (7.69)  | 47 (83.93)        |        |
| Pathology (Marsh)                                 |           |                  |        |
| 1                                                  | 54 (5.12)  | 47 (87.04)        | P = 0.02** |
| 2                                                  | 71 (6.73)  | 47 (66.20)        |        |
| 3                                                  | 964 (88.15)| 653 (70.29)       |        |
| 3a                                                 | 138 (17.95)| 97 (70.29)        | P = 0.37a |
| 3b                                                 | 253 (32.90)| 169 (66.80)       |        |
| 3c                                                 | 376 (48.89)| 270 (27.00)       |        |
| Type of diseases                                   |           |                  |        |
| Seropositive CD                                    | 1111 (96.86)| 784 (70.63)       | P = 0.87a |
| Seronegative CD                                    | 28 (2.44)  | 20 (71.43)        |        |
| IgA deficiency CD                                  | 4 (0.35)   | 3 (75.00)         |        |
| Others                                             | 4 (0.35)   | 2 (50.00)         |        |
| Patients classification                            |           |                  |        |
| Gastrointestinal                                   | 668 (61.12)| 497 (74.40)       | P < 0.001** |
| Non-gastrointestinal                               | 396 (36.23)| 264 (66.67)       |        |
| Screening                                          | 29 (2.65)  | 15 (51.72)        |        |
| TGA-IgA titer                                      | 190.84 ± 121.01 (rang 0.8, 834) | 191.04 ± 4.39 | P > 0.05 |

aFisher’s exact test, bPearson chi 2 test.
In this cohort 1,111 (96.86%) patients were seropositive celiac cases (positive by serology) and 28 (2.44%) were seronegative CD, this status not related to genders (P = 0.87). The mean ± SD of TGA-IgA titer was 190.84 ± 121.01 (rang 0.8, 834), mean of TGA-IgA titer not signiﬁcant between two genders (P > 0.05). Based on the results of the biopsies, more than 88% (n = 930) of patients had villous atrophy and 48.89% of them were type c (n = 376 Marsh 3c). This cohort classiﬁed to three presentations of celiac disease: typical 61.12%, atypical 36.23% and screened patients 2.65%, the presentations of CD related to gender (P < 0.001). The baseline characteristics of this celiac cohort are displayed in Table 1. Mostly patients (68.99%) presented by one clinical symptom and one third of them (n = 361) presented by 2 or more clinical symptoms at the time of diagnosis. The first common GI symptoms of CD were dyspepsia 22.26% and diarrhea 12.94%. Growing problem 9.92%, weight loss 8.80% and anemia 7.51% were others ﬁrst clinical symptoms in these patients. Also dyspepsia 12.97%, diarrhea 5.58%, anemia 5.24% and constipation 2.49% were secondly main clinical symptoms in this cohort. The main symptoms (chief complaint) at the time of their diagnosis are shown in Table 2. The nervous problems were the most concomitant disorders in celiac patients, as 57.76% of evaluated cases (n = 779) had a psychiatric disorder. Anxiety disorder (9.07%) and depression (8.31%) were the most common type of these psychiatric disorders. Unadjusted models show females more likely have nervous problems (OR = 1.37, CI 95% 1.00, 1.87) than male patients. Liver disease were seen in more than 22% of evaluated cases (n = 724), and this disorder not related to gender (OR = 0.88, CI 95% 0.54, 1.16), the most common of liver disease, was nonspeciﬁc abnormal alanine aminotransferase (ALT) (53.70%). Osteopenia have seen in 28.23% of CD patients, although odds of female are more likely to bone loss than male (OR = 1.51, CI 95% 1.01, 2.27). Other common disease in this cohort were oral aphtha (n = 301, 31.85%), and this not related to gender of patients (OR = 0.94, CI 95% 0.69, 1.27).

More than half of evaluated cases (n = 485, 54%) were anemic, based on their laboratory tests; and odds of anemia in female were two time more than male (OR = 2.09, CI 95% 1.56, 2.81).

The skin problems was seen in 23.53% of CD patients, that were include dermatitis herpetiformis (3.98%) and others skin problems (19.55%). Some concomitant immune and nonimmune disorders are shown in Table 3.

**Discussion**

This is the first large cohort study in the northeastern region of Iran evaluating the clinical manifestations and concomitant conditions in 1,164 celiac disease patients. In this study, most of our cases were among adults with the mean ﬁrst visit age of 29.67 years, ranging from 1 to 76. CD can present in all ages, and gluten intolerance can happen later in life even after age 60. As expected, CD was predominately in female in our cohort (F:M ratio 2.40). In our cohort common type of CD disease was gastrointestinal, interestingly, 2.65% of total cohort was diagnosed by CD screening, which is lower than previous reports (5–21%). The most common GI symptom was dyspepsia, which is different from the dominant presentation in children. These results are in line with other studies, which reported CD classic symptoms prevalence ranging from 34 to 85.2%. There are some reports of a notable trend of changing presentation of CD from classic to non-classic. For instance, reports in 1985 found 85.2% of patients to present with diarrhea, whereas in 2003–2013, presentation with diarrhea was estimated at 37.4%. This trend could be explained by the increasing awareness of clinicians from the atypical presentations of CD. In our study, only 12.94% had presented by diarrhea.

In our study, 31.01% of patients reported more than one speciﬁc clinical symptoms of CD disease. The main symptom that presented as ﬁrst or secondary clinical symptoms were include dyspepsia (35.23%), diarrhea (18.52%), anemia (12.75%), growing problems (9.92%), weight loss (8.80%), and flatulence (6.73%). Dyspepsia is not fully investigated in the literature as a symptom of CD. A notable percentage of CD patients are diagnosed incidentally through endoscopy for dyspepsia. Therefore, it could be concluded that our present knowledge of CD presentation is inadequate. Although there is some evidence of a high prevalence of dyspepsia in CD patients, especially in our region, most previous cohorts have not considered dyspepsia as a CD symptom. The occurrence of other presentations in our cohort were lower than previous finding, estimating the prevalence for diarrhea, weight loss, and abdominal pain to be at 27–64%, 28–56%, and 30–34%, respectively. Additionally, constipation and reﬂux were 5.51% and 4.06% which ranged between 1–13% and 12–14% in other studies. Type of disease was seropositive in 96.86% of CD patients, 2.44% of CD patients was seronegative which is in line with other studies that estimated prevalence of seronegative patients between 1.7–5%. The prevalence of IgA deﬁciency in our general population is not determined, but 0.35% of these patients had IgA deﬁcient.
Although most previous studies report 5–10% DH cases within CD patients, two larger studies reported percentages of 9.8%\(^3\) to 3.2%\(^2\) and decreasing prevalence of DH during last decade, probably because of early diagnosis of celiac disease. In our study 3.98% of patients had DH.

There has been a lot of research done investigating the association of CD in other autoimmune disorders such as diabetes and hypothyroidism, but few studies evaluate the prevalence of such autoimmune disorders in CD patients. In this study prevalence of hypothyroidism was estimated 15.09\%, which is in accordance with the current literature (10–30\%).\(^6,9,30,34\) The association between diabetes type 1 and CD is widely explored, Our study showed a high prevalence of diabetes type 1 in CD patients (5.78\%), which is supported by previous findings (3.2 to 10\%) of CD patients.\(^2,4,23\) Clinical guidelines recommend screening for CD in patients with autoimmune liver disease or chronic liver disease.\(^41\) In this cohort nervous problems were common concomitant disorders (57.43\%) in CD patients that more reported in female than male (OR = 1.37). The common nervous problems include anxiety disorder (9.07\%) and depression (8.31\%), although previous studies have found an increased risk of osteopenia and fragility fractures in celiac patients.\(^63–65\) A meta-analysis

| No. of evaluated patients | Type of diseases | \(n\) | Unadjusted OR CI 95% (f/m) |
|--------------------------|-----------------|------|-------------------------|
| Thyroid diseases \(n = 623\) | Without disease | 516 (82.83) | 1 |
| | Hypo Thyroid | 94 (15.09) | 0.77 (0.49, 1.20) |
| | Hyper Thyroid | 13 (2.09) |
| Skin problem \(n = 578\) | Without disease | 442 (76.47) | 1 |
| | Dermatitis herpetiformis | 23 (3.98) | 0.79 (0.52, 1.21) |
| | Others skin problem | 113 (19.55) |
| Nervous problem \(n = 779\) | Without disease | 338 (42.57) | 1 |
| | Depression | 66 (8.31) | 1.37 (1.00, 1.87)* |
| | Anxiety disorder | 72 (9.07) |
| | Headache | 44 (5.54) |
| | Others | 98 (12.34) |
| | Undetected problems | 176 (22.17) |
| Liver disease \(n = 724\) | Without disease | 562 (77.62) | 1 |
| | 1 ALT abnormality | 87 (12.02) | 0.80 (0.54, 1.16) |
| | Fatty liver | 42 (5.80) |
| | 2 AIH | 14 (1.93) |
| | 3 PBC | 5 (0.69) |
| | 4 PSC | 2 (0.28) |
| | Others | 12 (1.66) |
| Bone disease \(n = 627\) | Without disease | 450 (71.77) | 1 |
| | Osteopenia | 177 (28.23) | 1.51 (1.01, 2.27)* |
| Oral disease \(n = 945\) | Without disease | 644 (68.15) | 1 |
| | Aphthae | 301 (31.85) | 0.94 (0.69, 1.27) |
| Diabetes \(n = 1159\) | Without disease | 1092 (94.22) | 1 |
| | Type 1 | 67 (5.78) | 1.32 (0.74, 2.35) |
| Anemia \(n = 894\) | Without disease | 409 (45.75) | 1 |
| | Anemic | 489 (54.25) | 2.09 (1.56, 2.81)* |

Even screening for CD is recommended for patients with autoimmune liver disease or chronic liver disease.\(^41\)
on postmenopausal female and male with celiac disease reported the prevalence of osteopenia 39.6%. Bone loss is explained through malabsorption of calcium and vitamin D, leading to secondary hyperparathyroidism and metabolic bone disease. In addition, anemia was common in more than half of CD patients, in accordance to previous reports (8–50%). Also odds of anemia in female patients was twice more than male (OR = 2.01).

Conclusion
The classic type is common type of CD in northeast Iran. Dyspepsia, diarrhea and anemia main clinical symptoms in these patients, consequence we recommended to screening for CD in cases without classic symptoms, such as dyspepsia. Nervous problem, bon disease and anemia important concomitant disorders that more seen in female CD patients.

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Appendices

List of Abbreviations
Celiac disease (CD), Irritable bowel syndrome (IBS), Tissue transglutaminase (TG A), Anti-tissue Transglutaminase-IgA (TGA-IgA), Deamidated gliadin peptide (DGP), Common variable immunodeficiency (CVID), Gluten free diet (GFD), Alanine amino transferase (ALT), Gastrointestinal (GI)

Ethics Approval and Consent to Participate
The study was approved by the Ethics Committee of Mashhad University of Medical Sciences.

Consent for Publication
Not applicable.

Competing Interests
The authors declare that they have no competing interests.

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Authors’ Contributions
• Conceptualization; A. G.
• Data curtain; AG
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• Supervision & Validation; A.G.
• Roles/Writing original draft; A.G.K.R, F.A., B.Sh.
• All authors have read and approved the final manuscript.

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