Seroprevalence of Celiac Disease in Patients with Presumed Diagnosis of Diarrhea Predominant Irritable Bowel Disease

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Öz

Amaç: Diyare ağırlıklı irritabl barsak sendromu (İBS-D) hastalarında çölyak hastalığı (ÇH) seroprevalansının belirlenmesi

Yöntem Bu kesitsel tek-merkezli çalışmaya, İBS-D tanısı konulmuş 100 hasta (ort(SS) yaş: 42.8(16.8) yıl, %64.0'ü kadın) dahil edildi. Hastaların demografik özellikleri, sigara içme durumu, eş-zamanlı psikiyatrik hastalık varlığı ve kan biyokimyası sonuçları kaydedildi. Anti-doku transglutamaz(anti-tTG) antikorları (anti-tTG IgA ve anti-tTG IgG) ve endomisyum antikoru (anti-EMA) temelinde ÇH seroprevalansı belirlenerek; seropozitif ve seronegatif hastalar demografik özellikler ve laboratuvar bulguları açısından karşılaştırıldı.

Bulgular Hastaların %17'sinde anti-tTG IgG, %12.0'sinde anti-EMA ve %7'sinde anti-tTG IgA antikoru pozitif olarak saptandı. Hastaların 17(%17.0)'sinde en az bir antikor pozitifliği mevcut olup, bu hastaların 3(%3.0)'ünde tek değer, 9 (9.0%)'unda iki değer [2(%2.0) hastada anti- tTG IgA + anti-tTG IgG, 7(%7.0) hastada anti-tTG IgG + anti-EMA] ve 5(%5.0) 'inde ise üç değer (anti-tTG IgA + anti-tTG IgG + anti-EMA) üzerinden pozitiflik saptandı. ÇH seronegatif ve seropozitif hastalar arasında cinsiyet, aktif sigara içiciliği, eş-zamanlı psikiyatrik hastalık varlığı ve laboratuvar bulgular açısından anlamlı bir farklılık gözlenmedi.

Sonuç Sonuç olarak, bulgularımız ÇH serolojik bulgularının İBS-D hastalarının önemli bir kısmında pozitif olduğunu göstermekte ve dolayısıyla IBS-D hastalarında ÇH için "test ve tedavi et" stratejisinin faydalı olabileceğine işaret etmektedir.

Anahtar Kelimeler: Diyare ağırlıklı irritabıl bağırsak hastalığı, çölyak hastalığı, seroloji,dokutransglutaminaz antikorları,antiendomisium antikorları

Abstract

Object This study aims to determine seroprevalence of celiac disease (CD) in patients with presumed diarrhea predominant irritable bowel disease (IBS-D).

Methods A total of 100 patients with presumed IBS-D (mean(SD) age: 42.8(16.8) years, 64.0% were females) were included in this cross-sectional single-centre study. Data on patient demographics, smoking status, co-morbid psychiatric disorders and blood biochemistry were recorded. Seroprevalence of CD specific anti-tissue transglutaminase (anti-tTG) antibodies (anti-tTG IgA and anti-tTG IgG) and endomysial (EMA) antibody were determined, while demographic characteristics and laboratory findings were compared between CD seronegative and seropositive patients.

Results Anti-tTG IgG antibody was positive in 17.0% of patients, as followed by anti-tTG IgA antibody positivity in 7.0% and anti-EMA antibody positivity in 12.0% of patients. Positive findings for at least one antibody was noted in 17(17.0%) patients including positivity for single antibody in 3(3.0%) patients, two antibodies in 9(9.0%) patients and three antibodies in 5 (5.0%) patients. No difference was noted between seropositive and seronegative patients in terms of gender, active smoking, co-morbid psychiatric disorder and laboratory findings.

Conclusion In conclusion, our findings revealed that non-negligible percentage of patients with suspected IBS-D had positive serological findings for CD and thereby emphasize that "test and treat" strategy for CD in patients with presumed IBS-D may be worthwhile.

Key words: diarrhea predominant IBS; celiac disease; serology; anti-tissue transglutaminase antibody; endomysial antibody

Introduction

Irritable bowel syndrome (IBS), a functional gastrointestinal disorder characterized by chronic abdominal pain or discomfort associated with changes in bowel habits and a lack of physical abnormalities, biomarkers, or radiologic findings specific for the disease; is frequently encountered in primary and secondary care [1,6]. Consistent with worldwide prevalence of the disease that ranges from 5% to 20% in the general population [1,2], studies from Turkey have estimated the prevalence of IBS in the general population to range from 7.4–19.1% [7,9].

The diagnosis of IBS is based solely on a positive history of gastrointestinal symptoms according to the Rome III criteria [10]. The probability of detectable organic disease to account for the symptoms has been considered to be very low [11] in patients fulfilling the IBS criteria that reliably exclude organic disease with a positive predictive value of 98% [12]. Accordingly, while IBS is closely associated with other functional digestive and non-digestive disorders [13], a careful medical history has considered to be critical in the diagnosis of IBS. Hence performing a limited battery of tests to exclude common organic diseases masquerading as IBS has been recommended, since performing a series of useless and/or expensive diagnostic tests rarely alters the clinical impression[11,14,15].

Celiac disease (CD) is a chronic autoimmune disorder related to a permanent intolerance of gluten that can frequently result in symptoms similar to IBS and has an estimated prevalence of 0.7-1% in Western populations [16,20]. Hence testing for underlying CD in IBS patients has been considered to be an exception. Accordingly, the most recent evidence-based guidance document on the management of IBS offered by the American College of Gastroenterology (ACG) IBS Task Force recommended the inclusion of routine serological screening for in the diagnostic algorithm among patients with clinical features suggestive of diarrhea predominant IBS (IBS-D) or IBS with a mixed bowel pattern (IBS-M) [21], while this has not yet been universally accepted.

Recent epidemiological data indicate an increase in the prevalence of CD affecting approximately 1% of the general population as well as a remarkable change in the age of onset with increase in the number of newly diagnosed adults [22,25]. While limited data are available, estimated prevalence of CD in Turkey lies between 0.99–1.3% in Turkey, CD serology was reported to be positive in 1.3% of the general population, which seems to be higher than reported in Western countries [28]. In fact, the incidence of CD in patients with IBS was reported to be much higher than that expected in the general population [33], while considered to be even more prevalent in patients with suspected IBS-D [30]. Biopsy-proven CD was reported to be four [31] to seven [30,32] times likely and serologically-proven CD to be three times likely 30 in cases meeting the diagnostic criteria for IBS compared with controls without IBS.

Given the availability of noninvasive serologic tests with a high degree of sensitivity and specificity in the diagnosis of CD such as anti-tissue transglutaminase (anti-tTG) antibodies (anti-tTG Ig A and anti-tTG Ig G) and anti-endomysial (anti-EMA) antibody [30-35], it has been estimated that “test and treat” strategy for CD in patients with IBS, particularly in IBS-D, may be beneficial and cost-effective in clinical practice [15].

Therefore, the present single-centre cross-sectional study was designed to determine seropreva-

lence of CD among internal medicine outpatients with presumed IBS-D based on Rome III criteria.

Materials and Methods

A total of 100 consecutive patients (mean(SD) age: 42.8(16.8) years, 64.0% were females) who referred to internal medicine clinics of Recep Tayyip Erdogan University Faculty of Medicine with a presumed diagnosis of IBS-D between Jan 2013 and Jan 2014 were included in this cross-sectional single-centre study. Patients aged 18-65 years, with suspected IBS-D subtype based on Roma III diagnostic criteria 10 and Bristol stool scale 3 and without prior diagnosis of CD were included in the study. To be aged <18 or >65 years, previously diagnosed with inflammatory bowel disease, CD or malabsorption syndromes such as Whipple disease, food intolerance, abetalipoproteinemia and cystic fibrosis, presence of co-morbid endocrine diseases such as diabetes, hyperthyroidism, pheochromocytoma and vipoma, malignancy and concomitant treatments such as anti-diabetic and antihypertensive agents were the exclusion criteria.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee.

Study parameters

Data on patient demographics (age, gender), smoking status, co-morbid psychiatric disorders, blood count (hemoglobin, g/dl; hematocrit ,%), and blood biochemistry (glucose; g/dl), aspartate aminotransferase (AST; U/L), alanine aminotransferase (ALT; U/L), creatinine (mg/dl), total cholesterol (mg/dl), low density lipoprotein-cholesterol (LDL-c; mg/dl), high density lipoprotein-cholesterol (HDL-c; mg/dl), triglyceride (mg/dl), calcium (Ca; mg/dl), Fe (µg/dL), total iron binding capacity (µg/dL), total protein (g/dl), albumin (g/dl), thyroid stimulating hormone (TSH; IU/ml) and erthyrocyte sedimentation rate (ESR; mm/h) were recorded. Seroprevalence of CD was determined based on anti-tTG IgA, anti-tTG IgG and anti-EMA antibodies, while demographic characteristics and laboratory findings were compared between seronegative and seropositive patients.

Serological analysis

Venous blood samples were drawn in all patients following at least 8-hour fasting period. Anti-tTG Ig A and anti-tTG IgG antibodies were analyzed via Enzyme Linked Immunoabsorbant Assay (ELISA) method using a diagnostic kit (IMMCO42 diagnostics, ImmuLisaTM, Buffalo, NY, USA). Patients with anti-tTG Ig A, anti-tTG IgG and anti-EMA antibody levels of <10 EU/ml were considered to be seronegative, of 10-15 EU/ml to be borderline and of >15 EU/ml to be seropositive.

Statistical Analysis

Statistical analysis was made using computer software (SPSS version 17.0, SPSS Inc. Chicago, IL, USA). Chi-square (2) test and Fischer exact test were used for the comparison of categorical data and Mann Whitney U test was used for the analysis of numerical data. Data were expressed as "mean (standard deviation; SD)", minimum-maximum and percent (%) where appropriate. $p<0.05$ was considered statistically significant

Results

Patient characteristics

Of 100 patients included in the study, 64% were females and mean(SD) age was 42.8(16.8) years. Active smokers composed 25.0% of the study population and previous diagnosis of a psychiatric disorder was evident in 24.0%. There was no gender difference on age (mean(SD) 43.2 (17.5) years in females vs. 42.1(15.7) years in males) and the rate of psychiatric disorder, while significantly higher percentage of males than females were active smokers (55.5% vs. 7.8%, p=0.00); (Table 1).

Seroprevalence of CD

Anti-tTG IgG antibody positivity was the most common serological finding. Positive findings for at least one antibody was noted in 17 (17.0%) patients including positivity for two antibodies in 9(9.0%) patients (anti- tTG IgA + anti-tTG IgG in 2[2.0%] patients; anti-tTG IgG + anti-EMA in 7[7.0%] patients) (Table 2).

No difference was noted between seropositive and seronegative patients in terms of gender, active smoking, co-morbid psychiatric disorder and laboratory findings (Tables 2-3).

Discussion

Our findings in a cohort of patients with suspected IBS-D revealed positive serology for CD based on positive findings at least for one antibody in 17% of patients including anti-tTG IgG antibody positivity in 17.0%, anti-EMA antibody positivity in 12.0% and anti-tTG IgA antibody positivity in 7.0%. No significant difference was noted between patients with presumed IBS-D who were seronegative and seropositive for CD in terms of gender, the rate of active smoking and co-morbid psychiatric disorder as well as the laboratory findings.

Data from a systemic review of 6 studies by Spiegel et al. revealed the prevalence of CD in cohorts with symptoms suggestive of IBS to range from 0.7% to 11.4 % [19] along with higher likelihood of CD diagnosis in suspected IBS-D cases compared with matched controls [19,35].

In a recent meta-analysis of 13 studies by Ford et al., on the basis of anti-EMA or anti-tTG antibodies, CD seropositivity was shown in 41(4.0%) patients with symptoms suggestive of IBS that ranged from 0.0% to 11.4% in the different studies, while 7.0% in patients with IBS-D with three times more likely serological positivity in patients than in controls [36].

In a past study on the association of CD and IBS in adult Turkish population by Ozdil et al., anti-tTG IgA antibody was reported to be positive in 4 of 60 (6.6%) patients and anti-EMA antibody positivity in none of IBS patients 41. Also, normal findings on histopathological examination of duodenal biopsies excluded a diagnosis of CD and none of 40 control subjects had serological positivity for CD [40].

Similarly, 6 of 72 (8.3%) patients with IBS were reported to be positive for anti-tTG IgA and none for EMA antibody in a population based case-control US study by Locke et al. [37]. Similarly, testing for CD in IBS patients whose main complaint is diarrhea; bloating or abdominal distension has been suggested in a past study from Iran by Bakhshipour et al. which revealed 20 of 364(5.5%) patients with IBS to have anti-tTG IgA antibody positivity [38].

In another study from Turkey by Korkut et al. on the prevalence of CD in patients with IBS fulfilling

ROME III criteria, elevated levels of serum antigliadin IgA and IgG, and anti-tTG IgA antibodies were noted only in 2 of 100 (2.0%) patients along with histological evidence of CD on examination of duodenal biopsy [39]. Additionally, a lower prevalence was reported to be associated with composition of majority of the study population from constipation-predominant IBS patients [39].

Prevalence of anti-tTG IgA or anti-tTG IgG seropositivity for CD among healthy blood donors was reported to be higher (1.3%) in Turkey by Tatar et al. compared with data from Western countries 26. Likewise, in another study conducted with 188 patients with IBS-D in Turkey by Kuyumcu serological findings were reported to be positive for anti-tTG IgA antibody in 17 (9.0%) patients and for anti-tTG IgG in 6 (3.2%) patients 41. Also, 21(11.2%) patients were determined to be seropositive for either anti-tTG IgA or anti-tTG IgG antibody, exceeding the worldwide average [40].

Indeed, use of more extensive screening criteria including structural colon evaluations was reported to be associated with production of higher estimates for CS prevalence in IBS patients, than in studies lacking data on specific biochemical screening tests [15].

Accordingly, on the basis of serological tests, prevalence of CD in a remarkably high percentage of patients in the present cohort composed entirely of patients with presumed IBS-D support the stronger association suggested between IBS-D subtype and likelihood of positive CD serology 31. Notably, evaluation of 492 patients with symptoms of non-constipated IBS and 458 asymptomatic individuals in a prospective multi-center US study by Cash et al. revealed that patients with suspected IBS was 49% more likely to have abnormal celiac antibody tests on comprehensive antibody panel that included AGA, TTG, and EMA antibodies as well as HLA typing than healthy controls. However, this discrepancy was reported to ultimately alter the diagnosis in only 2/492 patients with suspected IBS based on esophagogastroduodenoscopy and duodenal biopsy analysis which confirmed the CD diagnosis in 0.41% of patients in the non-constipated-IBS group and 0.44% of controls [40].

Identification of anti-tTG antibody in 24 of 36 (66.6%) and anti-EMA antibody in 12 of 36 (33.3%) seropositive patients in our cohort seems quite consistent with the reported rates for anti-tTG (69.9%) and anti-EMA (27.7%) positivity among CD patients in the literature [25].

Notably, anti-EMA antibody positivity was the second most common serological finding, following the anti-tTG IgG positivity in our cohort of IBS-D patients who screened for CD serology. This seems contradictory both to the absence of anti-EMA positivity in IBS patients reported in some studies [36,37] and to the documented possibility that the anti-EMA is neither sufficiently sensitive (79%) nor specific (44%) in the subset of CD patients presenting with IBS symptoms.

Although our findings seem to indicate that anti-EMA and anti-tTG behaves similarly in identification of CD in IBS, at least in cross-sectional sample of patients in the IBS-D subtype; further investigation on the CS serology in patients stratified by IBS subtypes is needed to clarify whether serological tests behaves differently in different subsets of CS patients[15].

On the basis of well-established high prevalence of psychiatric comorbidities, particularly anxiety and depression, among patients with IBS, devoting particular attention to the presence of symptoms

suggesting anxiety or depression has been considered critical in the evaluation of a patient with a possible diagnosis of IBS[3]. Notably, psychiatric co-morbidity in IBS patient has been suggested to be readily performed if well-validated instruments such as the structured clinical interview for DSM-IV-TR are employed . Accordingly, all patients in our cohort had been admitted to psychiatry clinics for consultation either as a part of diagnostic work-up for IBD. Accordingly, previous diagnosis of a psychiatric disorder was evident in 24.0% of our patients with anxiety in 10.0% and depression in 13.0%. However, consistent with findings from the past studies [31,36,40], neither the co-morbid psychiatric disorder nor the gender and smoking status were determined as the factors influencing the likelihood of CD seropositivity in the present cohort of IBS-D patients.

Given that there are no available biological markers that clearly identify IBS patients, diagnosis of IBS has to be made via symptom-based criteria per se, which on the other hand is a highly recommended diagnostic strategy that reliably excludes organic disease with a positive predictive value of 98%.

However, given the positive serology for CD in remarkable percentage of our patients with IBS-D, our findings supports the statement that decision to screening for CD should be based on a consideration of the population prevalence of underlying CD 15 and in case of high population prevalence and persistently symptomatic IBS-D, serological tests for CD should be included in the diagnostic algorithm [15,21].

Indeed, since patients with CD often respond to a gluten-free diet, which can potentially improve symptoms, reverse the intestinal mucosal pathological changes and prevent long-term CD-related complications[18], failure to identify CD in a patient misdiagnosed with IBS means overlooking an alternative treatable diagnosis[15]. In this regard, it should be noted that all of our patients with seropositivity were referred to gastroenterology clinic for gastroscopic biopsy and patients who were also pathologically confirmed to have celiac disease were recommended with gluten-free diet.

Further investigation is necessary to conclude that CD is a significant problem in terms of misdiagnosis in IBS [15]. However, it should be noted that in a past study on cost-effectivity of testing for CS in patients with IBS-D by Spiegel et al., testing strategy was reported to have an acceptable cost when the prevalence of CS is above 1% and to be the dominant strategy when the prevalence exceeds 8% [15].

In this regard, our findings indicate the likelihood of CD seropositivity in a significant percentage of patients misdiagnosed with IBS-D and thus support the statement that physician awareness of the possibility of CD in patients presenting with IBS symptoms as well as atypical presentations of CD should be emphasized [25].

Certain limitations to this study should be considered. The likelihood of esophagogastroduodenoscopy and duodenal biopsy confirmed CD diagnosis has been considered to be at similar prevalence in IBS patients versus controls, despite relatively common presence of CD-associated antibodies in IBS patients [40]. Therefore, lack of a control group as well as data on esophagogastroduodenoscopy and duodenal biopsy analysis in patients who had CD-associated antibodies in our cohort seems to be the major limitations of the present study. Nevertheless, it should be noted that our patients

were tertiary care outpatients who had medical records on previous endoscopic and colonoscopic investigations carried out during diagnostic work-up. Also, it should be noted that the differences in the sensitivity and specificity of different anti-tTG antibody test kits and immunofluorescence tests such as EMA are subjected to inter-observer variability which seems to be minimized as far as possible in the present cohort given that all serological tests were performed by a single central laboratory.

In conclusion, our findings revealed that non-negligible percentage of patients with suspected IBS-D had positive serological findings for CD and thereby emphasize that "test and treat" strategy for CD in patients with presumed diagnosis of IBS-D may be beneficial in terms of successful management of the disease. Nevertheless, further work in larger scale cohorts stratified by IBD subtypes along with serologic and histopathological diagnostic methods seems necessary to conclude that CD is a significant problem in terms of misdiagnosis in IBS.

Conflict of Interest:
Authors declare no competing interest

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