Journal of Coloproctology

www.jcol.org.br

Original Article

Prevalence of anti-tissue transglutaminase antibodies in patients with irritable bowel syndrome in Duhok city

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ARTICLE INFO

Article history:
Received 14 August 2019
Accepted 25 August 2019
Available online 14 September 2019

Keywords:
Irritable bowel syndrome
Celiac disease
Rome III criteria
Anti-tissue transglutaminase

ABSTRACT

Background: Irritable bowel syndrome (IBS) is a common gastrointestinal disorder; celiac disease is an autoimmune enteropathy that can mimic any functional gastrointestinal disorder. The aim of this study is to estimate the prevalence of celiac disease antibodies (anti Tissue Transglutaminase—tTG) in patients with irritable bowel syndrome.

Patients and methods: This cross sectional study was conducted on 70 patients with irritable bowel syndrome fulfilling Rome III criteria who visited Azadi Teaching Hospital in Duhok city—Iraq. Patients were classified according to irritable bowel syndrome subtypes into: Diarrhoea Predominant (D-IBS), Constipation Predominant (C-IBS) and Mixed (M-IBS). IgA and IgG anti tTG were used to screen patients for celiac disease.

Results: A total number of 70 patients (44 females and 26 males) were included; their mean age was 33 years (SD ± 7.64). Five patients (7.1%) were found to have positive both IgA and IgG anti tTG. Three of them have had D-IBS and the other two had C-IBS. No one of the M-IBS patients tested positive.

Conclusion: The prevalence of anti tTG antibodies in irritable bowel syndrome is high. Patients with D-IBS should be screened for celiac disease.

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https://doi.org/10.1016/j.jcol.2019.08.001

Prevalência de anticorpos antitransglutaminase tecidual em pacientes com síndrome do intestino irritável na cidade de Duhok

Palavras-Chave:
Síndrome do intestino irritável
Doença celíaca
Critérios de Roma III
Antitransglutaminase tecidual

RESUMO

Introdução: A síndrome do intestino irritável (SII) é um distúrbio gastrointestinal comum; a doença celíaca é uma enteropatia autoimune que pode imitar qualquer distúrbio gastrointestinal funcional. O objetivo deste estudo foi estimar a prevalência de anticorpos contra a doença celíaca (antitransglutaminase tecidual - tTG) em pacientes com SII.

Pacientes e Métodos: Este estudo transversal foi conduzido em 70 pacientes com síndrome do intestino irritável que atendiam aos critérios de Roma III e se apresentaram ao Hospital de Ensino Azadi na cidade de Duhok, no Iraque. Os pacientes foram classificados de acordo com os subtipos de síndrome do intestino irritável em: predominantemente diarreia (D-SII), predominantemente constipação (C-SII) e mista (M-SII). IgA e IgG antitTG foram usados para rastrear pacientes com doença celíaca.

Resultados: Um total de 70 pacientes (44 mulheres e 26 homens) foram incluídos; a idade média foi de 33 anos (DP ± 7,64). Cinco pacientes (7,1%) apresentaram IgA e IgG antitTG positivos. Três deles tinham D-SII e os outros dois tinham C-SII. Nenhum dos pacientes com M-SII apresentou teste positivo.

Conclusão: A prevalência de anticorpos antitTG na SII é alta. A presença de doença celíaca deve ser avaliada em pacientes com D-SII.

Introduction

Irritable Bowel Syndrome (IBS) is an intestinal syndrome defined by abdominal discomfort and altered bowel habits without an organic cause. Throughout the world, about 10–20% of adults and adolescents have symptoms consistent with IBS, but only 10% of these consult their doctors because of symptoms. Most studies show a female predominance. In Asia, the prevalence of IBS varies between 3.5% and 25% with the lowest prevalence being reported from Iran and the highest from Japan.[1–4]

Risk factors for IBS are family history of IBS, a childhood sexual or physical abuse, food intolerance, oestrogen use, somatization traits, psychological distress and low birth weight.

The most widely accepted and studied risk factor is a history of infectious gastroenteritis, 7–30% of whom develop IBS.[1]

The pathophysiology is incompletely understood but biopsychosocial factors are thought to play an important role, along with luminal factors, such as diet and the gut microbial flora.

No clear diagnostic markers exist for IBS, thus the diagnosis of the disorder is based on clinical presentation, however individual symptoms are not useful for distinguishing IBS from alternative diagnoses and therefore clinical criteria have been proposed for the diagnosis of IBS.[1–3]

The Rome criteria, revised in 2005 (Rome III), is the latest consensus report proposed by the American Gastroenterological Association which provides an acceptable level of accuracy for the diagnosis of IBS in the absence of organic disorders (Box 1) According to the Rome III criteria, IBS subtypes (Box 2) had also been defined on the basis of predominant symptoms:

Box 1: Rome III criteria for diagnosis of IBS.

Diagnostic criterion[a]
Recurrent abdominal pain or discomfort[b] at least 3 days/month in the last 3 months associated with two or more of the following: 1. Improvement with defecation. 2. Onset associated with a change in frequency of stool. 3. Onset associated with a change in form (appearance) of stool.

[a]Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.
[b]"Discomfort" means an uncomfortable sensation not described as pain.

Box 2: Rome III classification for IBS subtypes.

1. IBS-C: Hard or lump stools at least 25% and loose (mushy) or watery stools <25% of bowel movements.
2. IBS-D: Loose (mushy) or watery stools at least 25% and hard or lumpy stools < 25% of bowel movements.
3. IBS-M: Hard or lumpy stools at least 25% and loose (mushy) or watery stools at least 25% of bowel movements.
4. Unsubtyped-IBS: Insufficient abnormality of stool consistency to meet for IBS-C, D or M.

Constipation predominant type (C-IBS), Diarrhoea predominant type (D-IBS), Mixed type (M-IBS) and Subtyped (U-IBS).[1–5]

Age over 50 years, weight loss, anaemia, nocturnal pain, presence of blood in stool and a family history of colorectal cancer are described as alarming findings and should prompt further evaluation in patients with IBS-like symptoms.[1–5]

It must be remembered, however, that patients commonly transit between these subgroups.

The symptoms of diarrhoea and constipation are commonly misinterpreted in IBS patients. Thus, many IBS patients who complain of "diarrhoea" are referring to the frequent passage of formed stools and, in the same patient population, "constipation" may refer to any one of a variety of complaints associated with the attempted act of defecation and not simply to infrequent bowel movements.[6]

Celiac Disease (CD), or gluten-sensitive enteropathy, is an inflammatory disorder of the small intestine induced by gluten in cereals (wheat, rye, barley and oats) in genetically susceptible persons. In its classic form, malabsorption of nutrients, chronic diarrhoea, weight loss and abdominal pain constitute the clinical picture. In atypical forms that may be more common than the classic presentation, less severe GI symptoms, such as abdominal distension, flatulence and constipation, and extra intestinal manifestations are predominant.[3,4,7]

Wheat (main source of gluten) has been the major staple food in the Middle East for many centuries and it is possible that the continuous and high level of exposure to wheat proteins has induced some degree of immune tolerance, leading to milder symptoms, which are misdiagnosed as IBS or unexplained GI disorders.[4]

A diagnosis of CD, unlike IBS, is based on the laboratory and histopathological findings, sometimes even in the absence of clinical symptoms. Immunoglobulin A (IgA) anti-tissue Transglutaminase (IgA-tTG), similar to IgA Antiendomysial Antibody (EMA), is highly sensitive (85%–95%) and specific (approximately 99%) for the diagnosis of CD.[3,5]

The protean manifestations of CD might significantly overlap with those of IBS. Undetected CD does not respond to standard treatment for IBS and untreated CD patients are at an increased risk for developing debilitating complications.[5]

Celiac disease should not be confused with Gluten-Sensitivity (GS) which is a condition of some morphological, immunological, or functional disorder that responds to gluten exclusion. The concept of GS incorporates a variety of pathological, immunological, and clinical scenarios that have been described recently, these include gluten sensitive diarrhea, immunological mucosal response to gluten in family members of celiac disease, persistently positive specific serology for celiac disease in the absence of defined enteropathy and subtle immunopathological changes in the intestine exposed to gluten. GS is an entity that lies between CD and IBS.[8]

Many gastroenterologists support the inclusion of CD screening tests as part of routine testing for IBS; however, this has yet to become a universally accepted recommendation. Therefore, the present study was designed to determine the prevalence of celiac antibody (anti-tTG) concentrations in IBS patients and to investigate whether their prevalence differ among varied IBS subtypes.[9]

Patients and methods

This cross-sectional study had been undertaken between October 2013 – March 2014. All patients presenting to the general internal medicine clinic in Azadi teaching hospital (Duhok city) complaining of gastrointestinal symptoms were asked for enrolment in this study.

The similarities between IBS and CD were explained to all patients and informed consents were obtained, then patients fulfilling Rome III criteria for IBS were evaluated for inclusion in the study and if included were classified according to subtypes of IBS: as Diarrhoea predominant IBS (D-IBS), Constipation predominant IBS (C-IBS), Mixed IBS (M-IBS) or Unsubtyped IBS (U-IBS).

Exclusion criteria were: age (>50 years), presence of one or more alarming symptom; weight loss, anaemia (haemoglobin below 12.5 g/dL), having a family history of inflammatory bowel disease or cancer, abnormal finding on abdominal examination and/or nocturnal diarrhoea)

Pregnant patients and subjects with any kind of malignancy, heart failure, chronic respiratory disease, significant liver disease, chronic renal failure, severe psychiatric disorders, metabolic or endocrine diseases were not included.

All patients underwent a complete physical examination. Laboratory evaluation included complete blood count to exclude anaemia (an alarming sign). Then sera of patients were used to measure Immunoglobulin A and Immunoglobulin G anti Tissue Transglutaminase antibodies (IgA and IgG anti tTG antibodies) as a screening test for celiac disease.

The method used was a solid-phase enzyme immunoassay for the quantitative and qualitative detection of antibodies against neo-epitopes of Tissue Transgltaminase (tTG) in human serum. The assay employing human recombinant transglutaminase cross linked with gliadin-specific peptides displays neo-epitopes of tissue tranglutaminase which ensures a significantly increased sensitivity and specificity of the test (Aeskulisa Ttg-A and Aeskulisa tTG-G, Wendelsheim, Germany). A value higher than 18 U/mL (for both IgA and IgG) was considered positive. Data were coded and analysed by Statistical Package for Social Sciences (SPSS) version 18 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 70 patients with IBS were included, 44 were females (62.9%) and 26 were males (37.1%). The mean age of the participants was 33 years.

Of the total 70 patients-based on stool consistency and bowel motion frequency of Rome III criteria—40 (27 females and 13 males), 12 (9 females and 3 males) and 18 (9 females and 9 males) were classified as C-IBS, D-IBS and M-IBS, respectively. No U-IBS patients were found in the study.

Neither gender (p-value = 0.093) nor age difference (p-value = 0.316) were identifiable among the various subtypes of IBS. The frequency and percentage of the subtypes are shown in Table 1.

Five patients (7.1%) tested positive for anti tTG (both IgA and IgG). The characteristics of patients with positive results

Table 1 – Frequencies and percentages of the IBS subtypes in the study.

	Frequency	Percentage
Constipation	40	57.1
Diarrhoea	12	17.1
Mixed	18	25.7
Total	70	100

Table 2 – The characteristics of patients with positive anti tTG.

Age	Duration/Chief complaint	Subtype	tTG-A (U/mL)	tTG-G (U/mL)
33 y	2 y/diarrhoea	D	30.8	19
20 y	1 y/distention	C	241.2	265.6
27 y	8 m/diarrhoea	D	19.3	18.4
45 y	8 m/diarrhoea	D	20.9	22.9
30 y	1 y/constipation	C	115.2	19.4

Table 3 – Cross tabulation demonstrating anti tTG percentages and frequencies in the IBS subtypes.

IBS subtypes	Anti Ttg Negative	Anti Ttg positive	Total
Constipation F (%)	38 (95%)	2 (5%)	40
Diarrheal F (%)	9 (75%)	3 (25%)	12
Mixed F (%)	18 (100%)	0	18
Total	65 (92.9%)	5 (7.1%)	70

are shown in Table 2 Patients with positive serology had the duration of their symptoms ranging from 8 months to 2 years (mean 12.8 months) and their age ranging from 20 to 45 years (mean 31 years).

Two of them (both are males) were having constipation dominant IBS which constitutes only 5% of the total C-IBS patients, the other three (two females and one male) were having diarrhea dominant IBS and they constitute 25% of the total D-IBS patients, this was regarded to be statistically significant (p-value = 0.05). Table 3 demonstrates anti tTG percentages and frequencies in the IBS subtypes.

Patients who tested positive for tTG were informed about their results and offered to undergo a gastroscopic examination to obtain a duodenal biopsy, but unfortunately no one volunteered so they were advised to adhere to gluten free diet with follow up visits in the next 3 months.

Discussion

To date, several presentations of CD have been identified: typical, atypical, latent and potential. It is widely believed that most patients with CD have obscure clinical and functional characteristics, labeling them as having latent disease or as potential Celiac patients.[10–12]

Missed diagnosis poses a risk for potential complications such as osteoporosis, infertility and malignancies. A gluten-free diet has been shown to decrease mortality and improve quality of life, even in asymptomatic patients.[13]

From the results shown we conclude that the prevalence of positive celiac serology in our study is 7.1%. The application of the Rome III criteria still could not exclude celiac disease on the basis of clinical and laboratory findings.

In our study we applied Rome III criteria, the main differences from Rome II criteria include; redefinition of the duration and frequency of the symptoms required *t* make the diagnosis and the inclusion of relief of symptoms after defecation as a diagnostic criterion. Subtypes were also updated.

The prevalence of CD in the general population lies between 0.02%–1%. In two recent cost-effectiveness analyses it has been postulated that serologic testing for CD in a population with a prevalence of around 1% would be cost-effective.[14,15]

Of course, since the patients in this study were not subjected to histopathological evaluation, it is not possible to comment on the true prevalence of celiac disease.

In a study from England by Sanders et al., 300 patients who were referred for secondary care with a suspicion of having IBS met the Rome II criteria for the disorder. They used AGA (Anti Gliadin Antibodies) and EMA to screen for CD. Sixty-six of the patients were found to be positive for EMA, while 14 patients (4.7%) had CD confirmed by biopsy (11 EMA positive, 3 EMA negative).[16]

In another primary care cross-sectional study by the same team, out of 1200 patients 123 met the Rome II criteria for IBS. Again AGA and EMA were used as screening tests and 3.3% of the patients had histopathological findings consistent with CD.[17]

Recently, Jadallah et al. from Jordan detected antiTG antibodies in 24 out of 742 previously uninvestigated patients who fulfilled the Rome II criteria for IBS. Duodenal biopsies confirmed the presence of CD in 3.23% of patients.[18]

More interestingly Hoshiyar et al. from Iran showed that the prevalence of celiac in patients with IBS is found to be 13.5% (14 out of 105) which seems to be the highest among the results from other studies done in the same country.[19]

Also Ford et al. in a meta analysis that comprised four studies demonstrated that the prevalence of biopsy proven CD among IBS patients is four times greater than controls.[20]

All the above mentioned studies concluded that screening IBS patients for CD is advisable.

On a different note, an American study by Locke et al. on 50 primary care patients diagnosed with IBS using Manning criteria, tTg antibody positivity was reported at 4%. Interestingly, they discovered that this rate was not different in patient with dyspeptic symptoms compared to those who were asymptomatic. They suggested that CD did not explain the presence of either IBS or dyspepsia in these subjects.[21]

In a Turkish study by Ozdil et al. on 60 patients completely fulfilling the Rome II criteria for IBS, antigliadin IgA positivity was observed in 4 patients However, normal findings on histopathological examination of duodenal biopsies excluded a diagnosis of CD.[22]

In Zobeiri et al. (a case control study) no difference existed between IBS patients and control in regard to celiac screening using IgA Ttg.[23]

In addition and from North America Cash et al. concluded in a case—control study that although CD-associated antibodies (including IgA tTG) are relatively common, the prevalence of CD among patients with nonconstipation IBS is similar to that among controls in a large US population.[24]

Finally Emami et al. from Iran demonstrated in their study that the prevalence of CD in patients with IBS might be significant but serum anti-tTG IgA antibody is not helpful in detecting CD in these patients.[25]

Though the American college of gastroenterologists recommends screening for CD in both D-IBS and M-IBS, there is no universal consensus on routine testing for CD in IBS patients and unfortunately, it is not always possible to identify patients with CD who present with IBS-like symptoms based on history and clinical evaluation alone.[20]

Conclusion and recommendations

The prevalence of anti tTG antibodies among patients with IBS is high and patients with D-IBS should be screened for CD, using anti tTG antibodies. Further studies with larger scales are needed to be done in the future with the aim to confirm the diagnosis of CD in IBS patients histologically.

Ethical approval

Ethical approval was granted from the Medical Board Committee.

Informed consent

An informed written consent was taken from the patients to be included in this study.

Conflicts of interest

The authors declare no conflicts of interest.

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