Is it reasonable to perform serological tests for celiac disease in patients with irritable bowel syndrome?

Czy u pacjentów z zespołem jelita nadwrażliwego zasadne jest wykonywanie testów serologicznych w kierunku celiakii?

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Key words: irritable bowel syndrome, gluten intolerance, serology.
Słowa kluczowe: zespół jelita nadwrażliwego, nietolerancja glutenu, serologia.

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Abstract

Introduction: Both the irritable bowel syndrome (IBS) and celiac disease (CD) are diseases whose incidence has increased significantly over the past several decades. Growing body of evidence suggests that in some IBS patients, the undiagnosed celiac disease can be the cause of their symptoms.

Aim: To determine the prevalence of gluten intolerance and celiac disease types in patients with irritable bowel syndrome.

Material and methods: The study was conducted among gastroenterological surgery patients with irritable bowel syndrome diagnosed based on Rome II criteria treated in the Gastroenterology Clinic of Regional Brodnowski Hospital in Warsaw. One hundred and fifty IBS subjects were randomly selected for serological tests – in each patient, serum IgA autoantibodies against tissue transglutaminase (anti-tTG) and gliadin (AGAs) concentration were determined. These tests were also performed among 50 healthy subjects who served as the control group. In 20 patients with positive serological tests results for celiac disease the duodenoscopy with duodenal mucosa biopsy was performed.

Results: The incidence of positive serological test results for celiac disease was significantly higher in IBS patients compared to healthy control (32 vs. 0, $p < 0.001$). Duodenal mucosa histology in all patients who agreed to duodenoscopy ($n = 20$) was normal.

Conclusions: In IBS patients, gluten intolerance occurs significantly more often than in the general population, so it is advisable to perform serological tests for celiac disease in these patients. The most common celiac disease form in persons with IBS is the latent.

Streszczenie

Wstęp: Zarówno zespół jelita nadwrażliwego (ZJN), jak i celiakia są schorzeniami, których częstość występowania znacznie się zwiększyła w ostatnich kilku dekadach. Coraz więcej danych przemawia za tym, że u części pacjentów z rozpoznanym ZJN przyczyną dolegliwości jest nierozpoznana choroba trzewna.

Cel: Określenie częstości występowania nietolerancji glutenu i celiakii u osób z rozpoznanym ZJN.

Materiał i metody: Badania przeprowadzono wśród pacjentów poradni gastrologicznej Wojewódzkiego Szpitala Bródnowskiego z ZJN rozpoznanym na podstawie Kryteriów Rzymskich II. U 150 losowo dobranych pacjentów z ZJN wykonano badania serologiczne w kierunku celiakii – w surowicy oznaczono stężenie autoprzeciwciał klasy IgA przeciwko tkankowej transglutaminazie (anty-tTG) i gliadynie (AGAs). Badania te przeprowadzono również u 50 zdrowych osób stanowiących grupę kontrolną. U 20 pacjentów z dodatnimi wynikami testów serologicznych wykonano duodenoskopię z pobraniem wycinków z błony śluzowej dwunastnicy.

Wyniki: Częstość występowania dodatnich testów serologicznych w kierunku celiakii u pacjentów z ZJN była istotnie większa niż w grupie kontrolnej (32 *vs* 0, $p < 0{,}001$). Obraz histopatologiczny błony śluzowej dwunastnicy u wszystkich osób, które wyraziły zgodę na duodenoskopię, z grupy z dodatnim mianem przeciwciał anty-tTG i/lub AGAs ($n = 20$) był prawidłowy.

Wnioski: Nietolerancja glutenu u osób z ZJN występuje istotnie częściej niż w populacji ogólnej, dlatego też zasadne jest wykonywanie u nich testów serologicznych w kierunku celiakii. Najczęstszą postacią choroby trzewnej u pacjentów z ZJN jest forma latentna.

Introduction

Both irritable bowel syndrome (IBS) and celiac disease (CD) are diseases whose incidence has increased significantly over the past several decades. In the case of celiac disease, it is undoubtedly associated with new diagnostic methods introduced in the 1990s – sensitive and specific serological tests – an assay of the anti-endomysial antibodies (EMA), and particularly antibodies against tissue transglutaminase (anti-tTG) [1].

A growing body of evidence suggests that in some IBS patients, their symptoms can be caused by undiagnosed disorders such as a pro-inflammatory state, food allergy/intolerance, or celiac disease [2-4]. A paper published in 2001 [5] argues that celiac disease occurs significantly more frequently in IBS patients than in the population without this syndrome. It seems that the incidence of CD among patients with IBS is 3-11% [6, 7]. Ford *et al.* [8] performed a meta-analysis of studies carried out between 1950 and 2008 on the relationship between celiac disease and IBS and discovered that CD occurs four times more often in people with diagnosed IBS than among those without this syndrome.

Aim

The goal of this study was to determine the prevalence of gluten intolerance and celiac disease types in patients with irritable bowel syndrome treated in the Gastroenterology Clinic of the Regional Brodnowski Hospital in Warsaw.

Material and methods

The study was carried out in the years 2007-2009 with the approval of the Bioethics Committee at the National Food and Nutrition Institute in Warsaw. All the studied persons have given their written consent to participate in the study.

Study group characteristics

The study was conducted among gastroenterological surgery patients with irritable bowel syndrome diagnosed based on Rome II criteria treated in the Gastroenterology Clinic of the Regional Brodnowski Hospital in Warsaw. Of the total 395 patients with this syndrome, 100 patients were excluded based on the questionnaire survey because of comorbidities or taken medications which were contraindicated for performing serological tests. The following exclusion criteria were adopted: the presence of chronic inflammatory diseases, systemic and allergic diseases, treatment with steroids, antihistaminic, non-steroidal anti-inflammatory drugs, previous immunotherapy, and previous gastrectomy.

From among the remaining patients, every second patient was randomly selected for serological tests (150 people). The serological tests were also performed among 50 healthy subjects who served as the control group.

During the clinic visit, medical history on the occurrence of IBS symptoms (abdominal pain, diarrhea, constipation, flatulence) was collected. Patients were asked to estimate the frequency, duration and intensity of their symptoms. We established four levels of symptom severity:

0 – no symptoms;
1 – mild: awareness of symptoms, but they do not impede regular activity;
2 – moderate: symptoms impede regular activity;
3 – severe: symptoms make regular activity impossible.

Serological tests

Fasting blood was collected from the ulnar vein, then, after centrifugation, serum was frozen at –20°C. In each patient, serum IgA autoantibodies against tissue transglutaminase (anti-tTG) and gliadin (AGAs) concentration were determined.

Autoantibodies IgA anti-tTG and AGAs were marked with an enzyme immunoassay method (ELISA) using anti-tTG and anti-gliadin IgA AUTOSTATTM II tests.

Duodenoscopy

After obtaining serological test results, patients who had elevated IgA antibody concentration against tissue transglutaminase and/or against gliadin (n = 32) were selected. Thirty patients (two were unavailable because they changed the place of residence) were offered to have endoscopic examination performed. Twenty subjects agreed. In these patients duodenoscopy with duodenal mucosa biopsy was performed.

The lateral optic endoscope was introduced into the descending duodenum. Then, 3-5 mucosal slices were collected with biopsy forceps. These examinations were performed at the Endoscopy Laboratory of the Clinic of Metabolic Diseases and Gastroenterology.

Statistical analysis

To describe the distribution of the data, the following parameters were used: range, mean and standard deviation, median and quartiles, and frequency tables, depending on the type of variables. In order to identify independent risk factors for celiac disease, the multivariate logit regression model was used. The factors statistically significant at the 5% level were chosen with the stepwise elimination method.

The χ^2 test, Fisher's exact probability test and the test for trend for proportions were used for comparisons

Table I. Characteristics of IBS patients who underwent serological testing for celiac disease
Tabela I. *Charakterystyka pacjentów z IBS, u których wykonano testy serologiczne w kierunku celiakii*

Parameter	Total				Male				Female			
	n = 150 (100%)				*n* = 38 (25.3%)				*n* = 112 (74.7%)			
	X (SD)	Median	Min.	Max.	X (SD)	Median	Min.	Max.	X (SD)	Median	Min.	Max.
Age [years]	47 (15.3)	50	18	77	49 (15.8)	53	20	71	47 (15.1)	50	18	77
BW [kg]	69.9 (14.6)	69.0	40.0	115.0	81.8 (13.2)	80.0	56.0	115.0	65.9 (12.8)	64.0	40.0	103.0
BMI [kg/m^2]	25.4 (4.9)	24.8	16.0	40.9	26.4 (4.3)	25.9	17.7	37.1	25.1 (5.1)	24.5	16.0	40.9
WC [cm]	84.5 (12.8)	84.5	56.0	126.0	92.4 (13.0)	91.0	65.0	126	81.8 (11.6)	80.0	56.0	113.5

BW – body weight, BMI – body mass index, WC – waist circumference, IBS – irritable bowel syndrome

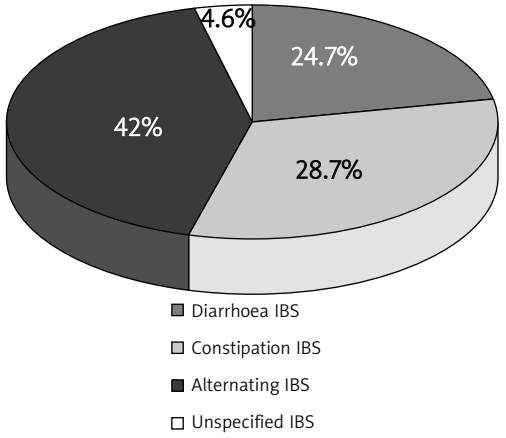


Fig. 1. The incidence of various IBS subtypes in the study group (*n* = 150)
Ryc. 1. *Częstość występowania poszczególnych postaci IBS w badanej grupie (n = 150)*

Table II. Structure of the study group depending on IBS intensity
Tabela II. *Struktura badanej grupy w zależności od stopnia nasilenia dolegliwości związanych z IBS*

IBS intensity	Number	Percentage
Mild	29	19.3
Moderate	57	38
Severe	64	42.7

Mild IBS intensity: awareness of symptoms, but they do not impede regular activity; moderate IBS intensity: symptoms impede regular activity; severe IBS intensity: symptoms make regular activity impossible

of proportions. To compare the distribution of categorical variables with ordered categories between independent observation groups, the Kruskal-Wallis test was applied.

Calculations were performed in Stata v.10 (Stata Statistical Software: Release 10 College Station, TX, Stata Corporation LP, 2007).

Results

Study group characteristics

The study group included 150 patients (38 men and 112 women) diagnosed with irritable bowel syndrome based on Rome II criteria. The median age of the subjects was 47 ±15.3 years (Table I).

The most frequent IBS form in the study group was the alternating form (42%), while the rarest was the unspecified form (4.6%). The incidence of the diarrhea and constipation forms was similar – 24.7% and 28.7%, respectively (Figure 1).

Over 42% of patients reported that their symptoms associated with IBS made their regular activity impossible (severe symptoms intensity), 38% stated that the impact was average (moderate symptoms intensity), while 19% believed that their IBS symptoms did not interfere with their regular activity (mild symptoms intensity) (Table II).

Serological tests

In the IBS group, 32 (21.3%) patients had elevated anti-tTG antibodies and/or AGAs serum concentration. Among them, six were men (18.7%) and 26 were women (81.3%) (Table III). Among women with IBS, serological tests for celiac disease were positive in 23.2%, among men in 15.8%.

The group of IBS patients who had positive serological test results for CD was called the CD(+) group, while the group of IBS patients with negative results was called the CD(–) group.

In the control group, no subject had elevated concentration of any type of tested antibodies (Table IV). Statistical analysis showed that the incidence of positive serological test results for celiac disease was significantly higher in IBS patients compared to healthy controls ($p < 0.001$).

Values of anti-tTG and AGAs in the group in which the concentration exceeded the upper limit are presented in Table V. In 5 subjects, concentrations of anti-tTG ranged between 7.1 U/ml and 7.9 U/ml, in 9 between 8.0 U/ml and 8.9 U/ml, and in 4 between 9.0 U/ml and

Table III. IBS patient number with positive serological tests for celiac disease – CD(+) group
Tabela III. *Liczba pacjentów z IBS, u których stwierdzono dodatnie wyniki testów serologicznych w kierunku celiakii – grupa CD(+)*

	Antibodies						Total	
	anti-tTG		AGAs		anti-tTG + AGAs			
	N	%*	*N*	%*	*N*	%*	*N*	%*
Total (*n* = 150)	24	16.0	5	3.34	3	2.0	32	21.3
Male (*n* = 38)	4	10.5	2	5.26	0	0	6	15.8
Female (*n* = 112)	20	17.9	3	2.68	3	2.7	26	23.2

**Percentage of persons in relation to the number of people in the group. Anti-tTG – antibodies against tissue transglutaminase, AGAs – antibodies against gliadin*

Table IV. Number of subjects with positive serological tests for celiac disease in the study group and control group
Tabela IV. *Liczba pacjentów z dodatnimi wynikami testów serologicznych w kierunku celiakii w grupie badanej i kontrolnej*

	Study group		Control group		Value of *p*
	N	%	*N*	%	
Total	32	21.33	0	0	< 0.001*
Male	6	15.79	0	0	
Female	26	23.21	0	0	

**Fisher test*

9.9 U/ml. In 6 people, the anti-tTG level was above 10 U/ml, but less than 18.7 U/ml. In 1 woman, the level of anti-tTG exceeded the value of 70 U/ml.

Statistical analysis revealed no significant differences in the incidence of positive serological tests for celiac disease depending on the IBS form and its symptoms' severity.

The average concentration of anti-tTG antibodies in the IBS CD(+) group was 12.2 ±11.9 U/ml, minimum value of 7.1 U/ml and maximum value of 70.3 U/ml (Table VI). In the IBS group, where the titer of anti-tTG antibodies did not exceed the upper normal range, namely in the CD(–) group, the average concentration of these antibodies was 2.5 ±2.0 U/ml. It is worth noting that in the control group, the mean concentration of anti-tTG antibodies was significantly lower than in the IBS CD(–) group (p = 0.019) and was 1.3 ±0.6 U/ml (Figure 2).

The average AGAs concentration in the IBS CD(+) group was 8.7 ±2.0 U/ml, while in the IBS CD(–) group it was 1.2 ±0.9 U/ml. As in the case of anti-tTG antibodies, mean AGAs concentration in the control group was significantly lower than in the IBS CD(–) group (p = 0.0001) (Figure 2).

Looking for other independent risk factors for celiac disease in IBS patients, the multivariate regression model was used. Gender, age, education, body mass index (BMI) and abdominal obesity were analyzed (Table VII).

Table V. The concentration of anti-tTG antibodies and AGAs in CD(+) group
Tabela V. *Stężenie przeciwciał anty-tTG i AGA w grupie CD(+)*

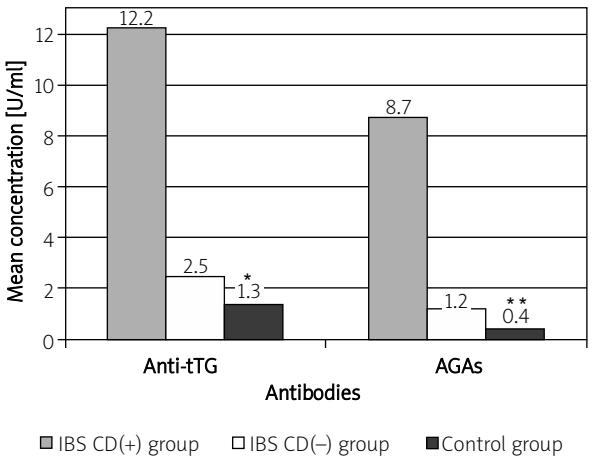
No.	Gender	Anti-tTG [U/ml]	AGAs [U/ml]
1	F	7.1	
2	F	7.2	
3	F	7.2	
4	F	7.6	
5	F	7.8	
6	F	8.0	
7	F	8.3	
8	F	8.3	
9	F	8.5	
10	F	8.6	
11	F	8.7	
12	F	8.8	7.6
13	F	8.9	
14	F	8.9	
15	M	9.1	
16	F	9.4	
17	F	9.7	
18	F	10.0	
19	F	10.4	
20	M	11.0	
21	F	12.2	
22	M	12.4	
23	F	12.8	
24	M	13.4	
25	F	16.5	8.3
26	F	18.6	
27	F	70.3	11.0
28	F		8.2
29	F		6.5
30	F		6.8
31	M		9.3
32	M		12.1

CD(+) group – IBS subjects with positive serological test results for celiac disease, anti-tTG – antibodies against tissue transglutaminase, AGAs – antibodies against gliadin, F – female, M – male

Table VI. Mean values of anti-tTG antibodies and AGAs concentration depending on the group
Tabela VI. *Średnie stężenie przeciwciał anty-tTG i AGA w zależności od badanej grupy*

Antibodies	Study group								Control			
	IBS CD(+)				IBS CD(–)							
	X (SD)	Median	Min.	Max.	X (SD)	Median	Min.	Max.	X (SD)	Median	Min.	Max.
Anti-tTG [U/ml]	12.2 (11.9)	8.9	7.1	70.3	2.5 (2.0)	2.1	0.0	6.9	1.3 (0.6)	1.1	0.6	3.9
AGAs [U/ml]	8.7 (2.0)	8.2	6.5	12.1	1.2 (0.9)	1.0	0.0	4.55	0.4 (0.4)	0.3	0.1	2.4

CD(+) group – IBS subjects with positive serological test results for celiac disease, CD(–) group – IBS subjects with negative serological test results for celiac disease, anti-tTG – antibodies against tissue transglutaminase, AGAs – antibodies against gliadin



*CD(+) group – IBS subjects with positive serological test results for celiac disease, CD(–) group – IBS subjects with negative serological test results for celiac disease, control group – healthy persons (without IBS), anti-tTG – antibodies against tissue transglutaminase, AGAs – antibodies against gliadin; *p < 0.05 – the difference between the IBS CD(–) and the control group, **p < 0.001 – the difference between the IBS CD(–) and the control group*

Fig. 2. Comparison of mean concentrations of anti-tTG and AGAs in the three analyzed groups
Ryc. 2. *Porównanie średnich wartości stężeń przeciwciał anty-tTG i AGA w trzech analizowanych grupach*

Table VII. Factors analyzed in terms of increasing the celiac disease risk in IBS patients
Tabela VII. *Czynniki poddane analizie pod kątem zwiększania ryzyka wystąpienia celiakii u pacjentów z IBS*

Factor	OR [95% CI]	Value of *p*
Gender		> 0.1
Age > 50 [years]		> 0.1
Education higher vs. others	2.7 [1.04, 6.94]	0.041
Abdominal obesity		> 0.1
BMI ≥ 25 vs. < 25 [kg/m^2]		> 0.1

BMI – body mass index

It was found that the only independent risk factor for celiac disease, statistically significant at 5%, was the education level. In people with higher education, the titer of anti-tTG and AGAs was elevated almost three times more often than in others (OR = 2.7, 95% CI = (1.04, 6.94), p = 0.041).

Duodenoscopy

Twenty patients agreed to duodenoscopy with duodenal mucosa biopsy and they had the test performed. Histological changes characteristic of celiac disease were not found in any subject. Duodenal mucosa histology in all patients was normal.

Discussion

In this study a total positive serological test for celiac disease occurred in 32 IBS patients (21.3%). In the control group, no one had elevated levels of any kind of tested antibodies – the frequency of positive serological tests for celiac disease was significantly higher in the study group.

Similarly high incidence (20-30%) of positive results of the serological test for celiac disease was obtained in other studies [5, 9, 10], while Mein *et al.* [11] and Jadallah and Khader [12] found elevated plasma level of anti-tTG autoantibodies in about 3% of IBS patients.

There are also studies which have not shown that positive serological test results for celiac disease are more frequent among IBS patients than in the general population [13, 14]. These studies covered primary care patients, in contrast to our study and the above-mentioned studies that covered patients treated at the specialist gastroenterology level. It can be assumed that higher incidence of positive serological tests for celiac disease should be expected among patients referred to a gastroenterologist, those whose symptoms are more troublesome and poorly responsive to treatment – which becomes the cause of a referral to a specialist.

We observed that the average concentration of anti-tTG and AGAs in IBS patients with a negative serological test result for celiac disease was significantly higher

than in the control group. It is difficult to determine whether this observation might be of clinical significance – other authors did not perform such comparisons. But perhaps this phenomenon may prove increased activity of the immune system in IBS patients – determination of this connection would require studies on larger patient groups.

Looking for features that would have predictive value for celiac disease among our IBS patients, we found that only the level of education was an independent statistically significant risk factor for celiac disease. Results of serological tests for CD were positive in people with university education almost three times more often than in other people. Other studies have not assessed the frequency of positive serological tests for celiac disease depending on the level of education. As we already know today, the development of gluten intolerance is the result of the interaction between genetic, environmental (dietary) and immunological factors. Perhaps higher education is an indirect indicator of a life characterized by high stress levels, which contributes to the dysfunction of the immune system.

Statistical analysis showed no significant differences in the frequency of positive serological tests for celiac disease depending on the IBS subtype and severity. Similarly, the results of a meta-analysis of studies concerning the connection between IBS and celiac disease [8] have shown that celiac disease is four times more common in people with IBS than in the general population and may be diagnosed in any form of this syndrome.

In this study, duodenoscopy with duodenal biopsy was performed in 20 subjects out of 32 IBS patients with positive serological test results for celiac disease. In all of them, the macroscopic picture of duodenal mucosa was normal, and the mucosa histopathological assessment did not show any abnormalities. Similar results were obtained by van der Wouden *et al.* [15]. In that study, out of 152 IBS patients, 36 subjects had elevated EMA serum levels and in none of them did duodenal mucosa histological examination show any features of celiac disease.

In other studies where positive serological test results for celiac disease were found in patients with irritable bowel syndrome, in some cases changes in duodenal mucosa characteristics of celiac disease were discovered. For instance, in the study by Sanders *et al.* [5] histological changes typical of celiac disease were found in 14 out of 66 subjects with positive serology. In another study [12] duodenal biopsy confirmed the presence of celiac disease in all patients with elevated anti-tTG antibodies (n = 24). The study by Zwolińska-Wcisło *et al.* [9] found that duodenal mucosa histopathology confirmed the diagnosis of celiac disease in 14 (35%) out of 40 IBS patients with abnormal anti-tTG antibody serum concentrations.

It can be assumed that our IBS patients suffered from latent celiac disease, so they belong to the group at high risk of developing full symptomatic celiac disease [16]. The results of the study by Alvisi *et al.* [17] showed that in patients with elevated concentration of anti-tTG, but normal small bowel mucosa, celiac disease with characteristic celiac histological changes of small intestine mucosa may develop over time. Therefore, it seems that people with latent celiac disease should have anti-tTG concentration tests and, if necessary, also duodenoscopy performed regularly.

Results of the Swedish study [18] suggest that gluten intolerance, despite the absence of changes in the duodenal mucosa, can cause symptoms such as diarrhea, abdominal pain and anemia. The same may apply to IBS patients with elevated anti-tTG/AGAs and normal duodenal mucosa. This would mean that the main cause of their IBS symptoms is gluten intolerance.

Those observations show that a lack of changes in histopathological examination of small intestine mucosa or the presence of mild changes in patients with positive serological test results for celiac disease does not excluded gluten intolerance, because it may develop into full symptoms later on.

It cannot be ruled out that an increase of anti-tTG antibody concentrations is a symptom of an autoimmune reaction damaging various organs, despite the absence of any abnormalities in duodenal mucosa histopathology [19]. The concept of the gluten syndrome [20] is very interesting. It extends the possibility of a harmful gluten effect beyond celiac disease. In other words, according to that approach, it is not necessary to prove histopathological changes in small intestine mucosa to diagnose gluten intolerance. For instance, gluten can harm the central nervous system by way of various mechanisms – by cross-reacting antibodies, immune complex disease, as well as by direct toxicity. Symptoms may include impaired regulation of the autonomic nervous system, cerebellar ataxia, hypotonia, mental retardation, learning difficulties, depression, migraine and other headaches [20].

In summary, our results show that in patients diagnosed with irritable bowel syndrome, regardless of its form, gluten intolerance is more common than in the population without this syndrome. On this basis, it appears that in IBS patients the most common form of celiac disease is the latent form.

Conclusions

In IBS patients, gluten intolerance occurs significantly more often than in the general population, so it is

advisable to perform serological tests for celiac disease in these patients. Thus, many patients could be treated earlier, thereby decreasing the number of complications and medical costs. The most common celiac disease form in individuals with IBS is the latent form.

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References

1. Iwańczak F, Iwańczak B. New guidelines for diagnosis and treatment of coeliac disease in children and adolescents. Prz Gastroenterol 2012; 7: 185-91.
2. Stankiewicz W, Rongies W, Bodera P, et al. Immunoregulatory disorders in irritable bowel syndrome. Centr Eur J Immunol 2011; 36: 267-74.
3. Traczyk I, Jarosz M, Tomasiuk R, et al. Concentration of IgG antibodies against food allergens in patients with irritable bowel syndrome and healthy individuals. Prz Gastroenterol 2011; 6: 382-7.
4. Nehring P, Mrozikiewicz-Rakowska B, Krasnodębski P, Karnafel W. Irritable bowel syndrome – a new approach to aetiopathogenesis. Prz Gastroenterol 2011; 6: 17-22.
5. Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult celiac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. Lancet 2001; 358: 1504-8.
6. Sanders DS, Patel D, Stephenson TJ, et al. A primary care cross-sectional study of undiagnosed adult celiac disease. Eur J Gastroenterol Hepatol 2003; 15: 407-13.
7. Shahbazkhani B, Forootan M, Merat S, et al. Celiac disease presenting with symptoms of irritable bowel syndrome. Aliment Pharmacol Ther 2003; 18: 231-5.
8. Ford AC, Chey WD, Talley NJ, et al. Yield of diagnostic tests for celiac disease in individuals with symptoms suggestive of irritable bowel syndrome. Arch Intern Med 2009; 169: 651-8.
9. Zwolińska-Wcisło M, Galicka-Latała D, Rozpondek P, et al. Frequency of celiac disease and irritable bowel syndrome coexistence and its influence on the disease course. Przegl Lek 2009; 66: 126-9.
10. Wahnschaffe U, Schulzke JD, Zeitz M, et al. Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. Clin Gastroenterol Hepatol 2007; 5: 844-50.
11. Mein SM, Ladabaum U. Serological testing for celiac disease in patients with symptoms of irritable bowel syndrome: a cost-effectiveness analysis. Aliment Pharmacol Ther 2004; 19: 1199-210.
12. Jadallah KA, Khader YS. Celiac disease in patients with presumed irritable bowel syndrome: a case-finding study. World J Gastroenterol 2009; 15: 5321-5.
13. Holt R, Darnley SE, Kennedy T, et al. Screening for celiac disease in patients with clinical diagnosis of irritable bowel syndrome. Gastroenterology 2001; 120:(Suppl. 1): A757.
14. Locke GR, Murray JA, Zinsmeister AR. Celiac disease serology in irritable bowel syndrome and dyspepsia: a population-based case-control study. Mayo Clin Proc 2004; 79: 476-82
15. Van der Wouden EJ, Nelis GF, Vecht J. Screening for celiac disease in patients fulfilling the Rome II criteria for irritable bowel syndrome in a secondary care hospital in the Netherlands: a prospective observational study. Gut 2007; 56: 444-5.
16. Craig D, Robins G, Howdle PD. Advances in celiac disease. Curr Opin Gastroenterol 2007; 23: 142-8.
17. Alvisi P, Marani M, Lambertini A, et al. Latent celiac disease in Emilia-Romagna paediatric population – 3 years surveillance. Dig Liver Dis 2008; 40: A75.
18. Ludvigsson JF, Brandt L, Montgomery SM. Symptoms and signs in individuals with serology positive for celiac disease but normal mucosa. BMC Gastroenterol 2009; 22: 57.
19. Freitag T, Schulze-Koops H, Niedobitek G. The role of the immune response against tissue transglutaminase in the pathogenesis of celiac disease. Autoimmun Rev 2004; 3: 13-20.
20. Ford RPK. The gluten syndrome: a neurological disease. Medical Hypotheses 2009; 73: 438-40.