Patients with serological markers of coeliac disease but without features of atrophy concerning villi of the small bowel mucosa – own observations

Pacjenci z obecnymi serologicznymi markerami celiakii, ale bez zaniku kosmków błony śluzowej jelita cienkiego – obserwacje własne

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Abstract

Aim: The purpose of the study was to determine the clinical characteristics of patients with positive serological tests for coeliac disease, in whom atrophic lesions of intestinal villi of the small bowel mucosa were not found.

Material and methods: The analysis comprised 30 patients, in whom positive IgA and/or IgG anti-endomysial antibodies were detected during the period from 2002 to the present time. Simultaneously performed endoscopic biopsy of the small bowel did not reveal atrophy concerning villi of the small bowel mucosa.

Results: The group of patients included 18 females and 12 males aged from 3 to 28 years. Eight patients did not show any gastrological symptoms. Three patients suffered from type 1 diabetes mellitus, two from Duhring's disease, one from ulcerative colitis, one from Crohn's disease, one from cystic fibrosis, but 8 patients showed family history loaded with the presence of coeliac disease or Duhring's disease. Recurrent abdominal pain (in 10 patients), chronic or recurrent diarrhoea (in 9 patients), alternating diarrhoea and constipation (in 1 patient), and constipation (in 2 patients) were the most often reported complaints or symptoms among symptomatic patients. Body mass deficiency occurred in 8 patients, short stature in 3 patients, enlarged abdomen circumference in 1 patient, skin lesions in 1 patient, and deficiency anaemia in 5 patients. A gluten-free diet was applied in 3 patients and clinical improvement was observed as a result. Positive anti-endomysial antibodies at least once were detected in 26 patients, using serum dilution of 1 : 20 or higher. Twenty seven patients did not reveal any histopathological lesions (M0) in a biopsy specimen of the small bowel mucosa, but

Streszczenie

Cel: Celem pracy była charakterystyka kliniczna pacjentów z dodatnimi testami serologicznymi w kierunku celiakii, u których nie stwierdzono zmian zanikowych kosmków jelitowych błony śluzowej jelita cienkiego.

Materiał i metody: Analizie poddano 30 pacjentów, u których od 2002 r. do chwili obecnej odnotowano obecność surowiczych przeciwciał antyendomyzjalnych w klasie IgA i/lub IgG, ale w wykonanej jednocześnie endoskopowej biopsji jelita cienkiego nie zaobserwowano zaniku kosmków błony śluzowej jelita cienkiego.

Wyniki: W grupie tej znalazło się 18 osób płci żeńskiej i 12 płci męskiej, w wieku 3–28 lat. U 8 nie stwierdzono żadnych objawów gastrologicznych. Trzech pacjentów cierpiało na cukrzycę typu 1, 2 – chorobę Dühringa, 1 – wrzodziejące zapalenie jelita grubego, 1 – chorobę Leśniowskiego-Crohna i 1 – mukowiscydozę. U 8 wywiad rodzinny był obciążony celiakią lub chorobą Dühringa. Wśród pacjentów objawowych najczęściej zgłaszanymi dolegliwościami lub objawami były: nawracające bóle brzucha (u 10), przewlekająca się lub nawracająca biegunka (u 9), naprzemiennie biegunka i zaparcie stolca (u 1) oraz zaparcie stolca (u 2). U 8 pacjentów odnotowano niedobór masy ciała, u 3 – niskorosłość, u 1 – powiększenie obwodu brzucha, u 1 – zmiany skórne, a u 5 – niedokrwistość niedoborową. U 3 pacjentów zastosowano dietę bezglutenową, po której obserwowano poprawę kliniczną. U 26 pacjentów przynajmniej raz stwierdzano obecność przeciwciał antyendomyzjalnych przy rozcieńczeniu surowicy 1 : 20 lub większym. U 27 pacjentów w bioptacie błony śluzowej jelita cienkiego nie odnotowano żadnych zmian histopatologicznych (M0), a u 3 pacjentów – limfocytozę śródnabłon-

3 patients showed intraepithelial lymphocytosis without atrophic lesions of intestinal villi and without crypt hypertrophy (MI). Concerning the group of 13 patients who underwent repeated endoscopic biopsy of the small bowel from the period of time from 1 year to 4 years, 12 patients did not present progression of histopathological lesions, but lesions of type IIIC of Marsh's classification were noted in 1 patient.

Conclusion: Patients with positive serum anti-endomysial antibodies, but without atrophic lesions of intestinal villi, need regular serological and histopathological control.

kową bez zmian zanikowych kosmków jelitowych i przerostu krypt (MI). W grupie 13 pacjentów, którzy od roku do 4 lat mieli wykonywaną powtórnie endoskopową biopsję jelita cienkiego, u 12 nie obserwowano progresji zmian histopatologicznych, a u 1 pacjenta stwierdzono zmiany typu IIIC wg Marsha.

Wniosek: Pacjenci z obecnymi surowiczymi przeciwciałami antyendomyzjalnymi, ale bez zmian zanikowych kosmków jelitowych wymagają systematycznej kontroli serologicznej i histopatologicznej.

Introduction

Coeliac disease is permanent gluten intolerance causing small bowel enteropathy of autoimmune origin in persons who are genetically predisposed. Diagnosis of coeliac disease and use of a gluten-free diet for the whole lifetime require proof of characteristic lesions in a biopsy specimen of the small bowel mucosa that abate after use of a gluten-free diet [1]. Histopathological lesions within the small bowel observed in coeliac disease evolve from almost unchanged small bowel mucosa with normal architecture of intestinal villi and increased number of intraepithelial lymphocytes (MI, meaning type 1 lesions according to modified Marsh's classification) *via* intraepithelial lymphocytosis and crypt hypertrophy (MII) to typical atrophy of intestinal villi (MIII) [2]. Diagnosis of coeliac disease is reliable in cases of demonstration of type MIII lesions, but it is controversial in cases of less advanced lesions of type MI and MII [3].

Detection of highly specific and sensitive serological tests such as anti-endomysial antibodies (EmA) and against tissue transglutaminase (tTG) facilitates selection to perform a small bowel biopsy in patients suspected of suffering from coeliac disease. We should remember that in the case of clinical suspicion of coeliac disease, even if serological tests are negative, the small bowel biopsy should be performed [3, 4].

The problem concerning management with patients in whom positive serum antibodies specific for coeliac disease were found, but atrophic lesions in the small bowel mucosa were not detected, still remains unsolved [5].

Aim

The aim of the study was clinical assessment of patients with positive serological tests for coeliac disease, in whom atrophic lesions of intestinal villi of the small bowel mucosa were not found.

Material and methods

All patients qualified for the analysis were hospitalised in the Chair and the Department of Paediatrics, Allergology and Gastroenterology of *Collegium Medicum* in Bydgoszcz and/or treated in the Outpatient Gastrological Clinic. These patients showed positive anti-endomysial antibodies in the serum and no atrophic lesions of intestinal villi in a biopsy specimen of the small bowel mucosa during the period from 2002 to the present time. During the same period coeliac disease was diagnosed according to modified ESPGHAN criteria in 111 patients.

Analysis concerning anti-endomysial antibodies in the serum was performed using the indirect immunofluorescence method with monkey oesophagus as antigen. Biopsy of the small bowel was performed endoscopically, collecting at least three biopsy specimens from different regions of the mucosa from the descending part of the duodenum. Modified Marsh's classification was used for histopathological assessment of biopsy specimens [2].

Results

Thirty patients aged from 3 to 28 years (average age 12.6 years), comprising 18 females and 12 males, fulfilled conditions to be included in the analysis. Patients' age ranged from 3 to 28 years (average age was 11.1 years) at the time of serological tests. Eight patients in the analysed group had no gastrological symptoms, but serological tests were performed due to affiliation to risk group of coeliac disease (type 1 diabetes mellitus in 3 patients, positive family history in 3 patients, Duhring's disease in 2 patients) or during analysis concerning the general population (2 children). Additionally, one patient – the sister of a patient with atypical coeliac disease – received a strict gluten-free diet due to clinical symptoms of classic coeliac disease and positive serological tests from the infantile period to 18 years of age, but currently during over two-year provocation with gluten still does not present any

clinical symptoms. Considering other patients, the most often reported complaints or symptoms were recurrent abdominal pain (in 10 patients), chronic or recurrent diarrhoea (in 9 patients), alternating diarrhoea and constipation (in 1 patient), and constipation (in 2 patients). Body mass deficiency occurred in 8 patients, short stature in 3 patients, enlarged abdomen circumference in 1 patient, skin lesions in 1 patient, and deficiency anaemia in 5 patients. Three patients suffered from type 1 diabetes mellitus, one from ulcerative colitis, one from Crohn's disease, one from cystic fibrosis and two from dermatitis herpetiformis. A gluten-free diet was applied in 3 patients apart from the normal picture of the small bowel mucosa and clinical improvement was observed as a result. Positive anti-endomysial antibodies at least once were detected in 26 patients, using serum dilution of 1 : 20 or higher. Only 4 patients presented positive anti-endomysial antibodies in lower serum dilution (1 : 10), including 2 patients in IgG class. Considering 25 patients, in whom serological tests were performed several times, the presence of anti-endomysial antibodies in the serum was found twice in 11 patients, and three times in 6 patients. Five patients did not reveal the presence of anti-endomysial antibodies in the serum in the second test and nor did 3 patients in the third subsequent serological test despite no change of applied diet.

Twenty seven patients did not reveal any histopathological lesions (M0) in the biopsy specimen of the small bowel mucosa, but 3 patients showed intraepithelial lymphocytosis without atrophic lesions of intestinal villi and without crypt hypertrophy (MI). Thirteen patients who underwent repeated endoscopic biopsy of the small bowel from the period of time from 1 year to 4 years included 12 patients with M0 lesions and 1 patient with MI lesions in the first biopsy. Progression of histopathological lesions were not observed in the second biopsy of the small bowel in 12 patients. Histopathological lesions of type IIIC of Marsh's classification were noted in the second biopsy in 1 asymptomatic patient, who followed a common diet for over two years and who was also the sister of a patient with coeliac disease. Characteristics of patients with positive serological tests for coeliac disease, but without atrophic lesions of intestinal villi, are shown in Table I.

Discussion

Latent coeliac disease is diagnosed in patients in whom while receiving a normal diet containing gluten, the small bowel mucosa is normal, but different earlier or later performed examination shows atrophic lesions of intestinal villi and these lesions withdraw after use of a gluten-free diet. Potential coeliac disease is defined as the disease phase before appearance of damage of the small bowel mucosa typical for coeliac disease [6]. Increased number of CD3+ lymphocytes, intraepithelial lymphocytes with receptor γ/δ, number of lymphocytes CD25+ and expression of ICAM-1 molecules are often found in the biopsy specimen of the small bowel mucosa in patients with potential coeliac disease despite a lack of atrophic lesions concerning intestinal villi [7]. Serological tests can help to identify patients with latent and potential coeliac disease. Anti-endomysial antibodies are the best indicator to predict damage of the small bowel mucosa [6]. Their presence in patients with a normal result of the histopathological examination concerning the biopsy specimen of the small bowel is rarely a false positive result, but more often indicates latent coeliac disease, predicting future occurrence of lesions typical for coeliac disease [6].

This study attempts to characterize patients in whom atrophic lesions of intestinal villi typical for coeliac disease were not found beside the presence of IgA and/or IgG anti-endomysial antibodies in the serum.

Only one patient from this group revealed the presence of typical damage of the small bowel mucosa in repeated small bowel biopsy and this fact entitled coeliac disease to be diagnosed and a gluten-free diet till the end of life to be recommended. Considering the very high specificity of anti-endomysial antibodies IgA-EmA assessed in the meta-analysis of Hill [8], it should be thought in 99% that all or nearly all remaining patients from the analysed group will develop in future damage of the small bowel mucosa typical for coeliac disease. Doubts first of all concern four children, in whom the titre of serum anti-endomysial antibodies was low, especially because their presence in IgG class was noted in two children and their presence was not proved in a subsequent test performed while on a normal diet containing gluten. A repeat test is indicated due to the possibility of false positive results concerning serum anti-endomysial antibodies (particularly in case of their presence found only in low dilutions of the serum) [4].

However, diagnosis of coeliac disease seems to be very probable in three patients in whom an increased number of intraepithelial lymphocytes was found in the biopsy specimen of the small bowel mucosa. It has been known for years that it constitutes the first and the most sensitive indicator of gluten's effect on

Table I. Characteristics of patients with positive anti-endomysial antibodies without villous atrophy of the small bowel mucosa
Tabela I. *Charakterystyka pacjentów z obecnymi przeciwciałami antyendomyzjalnymi bez zaniku kosmków błony śluzowej jelita cienkiego*

Number	Sex	Age	Age at the time of tests	Clinical symptoms	Titre of anti-endomysial antibodies	Result of the small bowel biopsy according to Marsh
1.	F	18 years of age	16 years of age	deficiency anaemia, gluten-free diet between 2 and 10 year of age (clinical suspicion of coeliac disease)	8 years of age – IgAEmA 1 : 20 16 years of age – IgAEmA 1 : 20 18 years of age – IgAEmA 1 : 80	 18 years of age – M0
2.	F	14 years of age	11 years of age	asymptomatic, positive family history (coeliac disease in sister)	IgAEmA 1 : 160 IgGEmA 1 : 160	MI + 40/100 IEL
3.	M	17 years of age	15 years of age	without gastroenterological symptoms, Dühring's disease at 5 years of age, gluten-free diet between 5 and 14 years of age	IgAEmA 1 : 640 IgGEmA 1 : 80	 MI + 20/100 IEL
4.	F	5 years of age	3 years of age	recurrent abdominal pain, alternating diarrhoea and constipation, body mass loss, recurrent aphthous stomatitis, hypertransaminasaemia	3 years of age – IgAEmA 1 : 160 3.5 years of age – IgAEmA(–) 5 years of age – IgAEmA(–)	 M0
5.	F	7 years of age	5 years of age	recurrent diarrhoea, deficiency anaemia, clinical improvement with use of gluten-free diet at 6 years of age	5 years of age – IgAEmA 1 : 80 7 years of age – IgAEmA 1 : 20	5 years of age – M0 7 years of age – M0
6.	M	15 years of age	10 years of age	body mass and height deficiency, Dühring's disease at 10 years of age, positive family history (coeliac disease in 2 sisters), poor use of gluten-free diet since 10 years of age	10 years of age – IgAEmA 1 : 80 10 years of age – IgAEmA 1 : 20	M0
7.	F	14 years of age	12 years of age	without clinical symptoms, screening tests in general population	IgAEmA 1 : 160	M0
8.	M	15 years of age	13 years of age	poor appetite, body mass deficiency, recurrent abdominal pain and diarrhoea, deficiency anaemia, Crohn's disease at 13 years of age	13 years of age – IgAEmA 1 : 40 13 years of age – IgAEmA 1 : 10	13 years of age – M0 13 years of age – M0
9.	F	20 years of age	18 years of age	gluten-free diet between 1 and 17 years of age (classic symptoms during 1 year of age, IgA-EmA 1 : 1280, without the small bowel biopsy), since 18 years of age gluten provocation test – without clinical symptoms, positive family history (coeliac disease in sister)	18 years of age – IgAEmA 1 : 640 19 years of age – IgAEmA 1 : 320 20 years of age – IgAEmA 1 : 160	18 years of age – M0 20 years of age – MIIIC
10.	F	10 years of age	9 years of age	height deficiency	9 years of age – IgA EmA 1 : 20 9 years of age – IgAEmA 1 : 5 11 years of age – IgAEmA(+)	9 years of age – M0
11.	M	17 years of age	14 years of age	type 1 diabetes mellitus, without gastroenterological symptoms	14 years of age – IgAEmA 1 : 160 16 years of age – IgAEmA 1 : 320 17 years of age – IgAEmA 1 : 80	14 years of age – MI + 40/100 IEL 17 years of age – MI + 40/100 IEL
12.	F	17 years of age	16 years of age	deficiency anaemia	16 years of age – IgAEmA 1 : 160 17 years of age – IgAEmA 1 : 40 17 years of age – IgAEmA 1 : 20	16 years of age – M0 17 years of age – M0
13.	F	12 years of age	11 years of age	body mass and height deficiency, recurrent diarrhoea since 10 years of age	11 years of age – IgAEmA 1 : 640 12 years of age – IgAEmA 1 : 640 12 years of age – IgAEmA 1 : 400	11 years of age – M0 12 years of age – M0
14.	M	13 years of age	12 years of age	without clinical symptoms, positive family history (coeliac disease in sister)	12 years of age – IgAEmA 1 : 40 13 years of age – IgAEmA 1 : 40	12 years of age – M0

Table I. Characteristics of patients with positive anti-endomysial antibodies without villous atrophy of the small bowel mucosa (cont.)
Tabela I. *Charakterystyka pacjentów z obecnymi przeciwciałami antyendomyzjalnymi bez zaniku kosmków błony śluzowej jelita cienkiego (cd.)*

15.	M	11 years of age	10 years of age	without clinical symptoms, screening tests in general population	9 years of age – IgAEmA(+/–) 10 years of age – IgAEmA 1 : 80	M0
16.	F	10 years of age	9 years of age	recurrent diarrhoea, abdominal pain	5 years of age – ↓ IgA, IgGEmA negative 9 years of age – IgGEmA 1 : 80	3 years of age – M0 5 years of age – M0 9 years of age – M0
17.	F	12 years of age	11 years of age	abdominal pain, body mass deficiency	11 years of age – IgAEmA 1 : 160 12 years of age – IgAEmA 1 : 20, IgAtTG(+)	11 years of age – M0 12 years of age – M0
18.	M	14 years of age	10 years of age	type 1 diabetes mellitus, without gastroenterological symptoms	10 years of age – IgAEmA 1 : 20 11 years of age – IgAEmA 1 : 20	MI + 30/100 IEL
19.	F	7 years of age	4 years of age	recurrent abdominal pains, diarrhoea, body mass deficiency, skin lesions, clinical improvement with use of gluten-free diet	3 years of age – IgAEmA 1 : 40 4 years of age – IgAEmA 1 : 640	3 years of age – M0 4 years of age – M0
20.	M	7 years of age	3 years of age	recurrent diarrhoea, poor body mass increase, deficiency anaemia, hypertransaminasaemia	3 years of age – IgAEmA(–) 3 years of age – IgGEmA – 1 : 10 4 years of age – IgGEmA(–)	M0
21.	F	9 years of age	5 years of age	recurrent abdominal pain	5 years of age – IgAEmA(–), IgGEmA – 1 : 10 6 years of age – IgGEmA(–)	M0
22.	M	8 years of age	4 years of age	recurrent abdominal pains, constipation	IgAEmA – 1 : 10	M0
23.	M	8 years of age	3 years of age	chronic diarrhoea, cystic fibrosis at 3 years of age	3 years of age – IgAEmA 1 : 40, IgGEmA 1 : 40 7 years of age – IgAEmA(–)	3 years of age – M0
24.	M	27 years of age	21 years of age	type 1 diabetes mellitus, without gastroenterological symptoms, positive family history (coeliac disease in brother)	21 years of age – IgAEmA 1 : 80, IgAtTG (+) 24 years of age – IgAEmA 1 : 80	21 years of age – M0 24 years of age – M0
25.	F	12 years	11 years	body mass and height deficiency, recurrent abdominal pain, positive family history (coeliac disease in father)	12 years of age – IgAEmA 1 : 5, IgAtTG(–) 12 years of age – IgAEmA 1 : 10 12 years of age – IgAEmA(–)	11 years of age – M0 12 years of age – M0
26.	F	28 years	28 years	recurrent diarrhoea, aphthous stomatitis, positive family history (Dühring's disease in father)	28 years of age – IgAEmA 1 : 320 IgAtTG(+), HLA DQ(+) 29 years of age – IgAEmA 1 : 20	M0
27.	F	9 years of age	9 years of age	recurrent abdominal pain, constipation, enlarged abdomen circumference	IgAEmA 1 : 20	M0
28.	F	10 years of age	10 years of age	chronic bloody diarrhoea, ulcerative colitis at 9 years of age	10 years of age – IgAEmA 1 : 80 10.5 years of age – IgGEmA 1 : 80	10 years of age – M0 10.5 years of age – M0
29.	M	3 years of age	3 years of age	poor body mass increase, positive family history (2 cases of coeliac disease in mother's family)	3 years of age – IgAEmA 1 : 1600 3.5 years of age – IgAEmA(–)	2 years of age – M0 3 years of age – M0
30.	F	13 years of age	13 years of age	recurrent abdominal pain, hypertransaminasaemia	10 years of age – IgAEmA(–) IgGEmA 1 : 20 13 years of age – IgAEmA(–)	13 years of age – M0

the mucosa of not only the small bowel, but also the stomach and large bowel [9]. The number of intraepithelial lymphocytes that should be acknowledged as the upper limit of the normal value is still a controversial matter. Marsh [2] did not give a definition of increased number of intraepithelial lymphocytes. The figure of 40 intraepithelial lymphocytes *per* 100 epithelial cells proposed by Oberhuber *et al*. [9] as the cut-off point was later arbitrarily reduced to 30/100 IEL. It has recently been suggested to decrease the normal value to 25 intraepithelial lymphocytes *per* 100 epithelial cells [10].

A diagnosis of potential coeliac disease also seems to be very probable in three patients with type 1 diabetes mellitus, 2 patients with Duhring's disease and children with a positive family history for coeliac disease (apart from a patient with definitive diagnosis of coeliac disease) or for Duhring's disease in first-degree relatives. At least two loading factors occur in two patients from this group (type 1 diabetes mellitus in one patient and classic coeliac disease in the patient's brother, but Duhring's disease and atypical coeliac disease in two sisters of the second patient). However, it has been known for years that patients with type 1 diabetes mellitus and dermatitis herpetiformis and relatives of patients with coeliac disease are risk groups of coeliac disease, particularly often concerning the potential or latent form [11]. Ninety percent of patients show histopathological lesions in the small bowel mucosa in the case of dermatitis herpetiformis, including 2/3 with atrophy of intestinal villi and 1/3 with increased number of intraepithelial lymphocytes [12].

Screening tests for coeliac disease in patients with type 1 diabetes mellitus should be performed at the time of diagnosis of diabetes mellitus, but then once a year due to seroconversion of antibodies specific for coeliac disease observed during a period of years [13]. Cases of latent coeliac disease in children with type 1 diabetes mellitus [14] and in first-degree relatives [15] are well documented. Inflammatory bowel diseases, like cystic fibrosis, are mentioned in the group of diseases that often coexist with coeliac disease [16], which is why also progression concerning lesions in the small bowel mucosa towards coeliac disease is probable in children suffering from these diseases.

Other patients underwent screening tests for coeliac disease due to reported complaints (recurrent abdominal pain, diarrhoea, poor body mass increase, short stature, iron deficiency anaemia) that often result in a clinical picture of classic or atypical coeliac disease [17].

Presence of anti-endomysial antibodies in serum of great dilution (several times in some patients) indicates the possibility that coeliac disease can occur in these patients. This fact demands systematic control concerning presence of anti-endomysial antibodies, but also periodic repeated small bowel biopsy with numerous biopsy specimens from different regions of the descending part of the duodenum. Similar management should be performed in two patients who underwent screening tests for coeliac disease as population examinations. These patients were the only ones in the analysed group to have no complaints.

The mechanism concerning the origin of clinical symptoms and laboratory abnormalities in patients with normal small bowel mucosa is difficult to explain. However, it seems that in patients with potential coeliac disease morphologically normal mucosa has functional defects responsible for disease symptoms [11]. Also, development of small bowel lymphoma is possible during the latent phase of the disease [18].

Rules concerning monitoring patients with positive serological tests and a normal result of the small bowel biopsy are still not determined.

Some examinations allow identification in this group of patients in whom histological lesions typical for coeliac disease will develop in future. These tests include assessment of number of CD3+ intraepithelial lymphocytes, number of intraepithelial lymphocytes with gamma/delta receptors or HLA DQ typing. These examinations are accessible with difficulty and they are rather used in scientific studies.

Genetic examination is the most accessible among these examinations and can exclude the possibility of coeliac disease, but the presence of HLA-DQ2 and/or HLA-DQ8 heterodimer does not definitively determine damage of the small bowel mucosa in future. We should remember that 39.5% of the general population also has one of these heterodimers characteristic for genetic predisposition to coeliac disease [19].

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