

ANNA SZAFIARSKA-POPŁAWSKA^{1, A, B, D-F}, MONIKA PARZEĆKA^{1, C, E},
RENATA KUCZYŃSKA^{2, C, E}

The Range of Lesions in the Small Intestine of Children with Celiac Disease Determined by Capsule Endoscopy

¹ Department of Pediatric Endoscopy and Gastrointestinal Function Testing,
Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

² Department and Clinic of Pediatrics, Allergology and Gastroenterology,
Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of article; G – other

Abstract

Background. Celiac disease is a chronic gluten intolerance which can cause small intestinal inflammatory lesions of different intensity, scope and distribution.

Objectives. The aim of the study was to assess the distribution and scope of lesions revealed by endoscopy in the small intestine of children and adolescents with untreated celiac disease.

Material and Methods. A total of nine patients aged from 15 to 18 years (average age: 16 years) were enrolled in the study, including seven girls and two boys who had been diagnosed with histologically confirmed celiac disease. Following a bowel cleansing all the patients were subjected to examination of the small intestine using an endoscopic capsule (EndoCapsule EC, Olympus, Tokyo, Japan).

Results. The examination was complete in eight of the patients. In six patients the capsule endoscopy revealed continuous lesions in the duodenum and the proximal small intestine. In one child continuous lesions occurred only in a short section of the bowel, within the duodenum. In one patient the abnormalities were located in the proximal small intestine without any lesions in duodenum. In one case, segmental lesions were observed in the distal small intestine, without any lesions in the duodenum or in the proximal part of the bowel. The results for the endoscopic markers of celiac disease were as follows: in all the patients a significant shortening or complete lack of villous structure was noted; in six patients scalloping was observed at the peaks of the circular folds; in three patients granulation was observed; and in three patients a mosaic mucosal pattern was noted.

Conclusions. The most frequent type of lesions revealed by capsule endoscopy in pediatric patients with untreated celiac disease seems to be continuous lesions in the duodenum and the proximal small intestine. Some patients can develop macroscopic lesions (and probably microscopic ones as well) that are beyond the reach of traditional endoscopy. In such cases, capsule endoscopy can help to determine and diagnose celiac disease and to establish the need for lifelong dietary treatment (*Adv Clin Exp Med* 2014, 23, 5, 785–790).

Key words: celiac disease, capsule endoscopy, children.

Celiac disease is a systemic disease of immunologic background caused by gluten and gluten-associated prolamins in people with genetic predispositions. Its characteristics include a variable clinical picture, the presence of specific antibodies of the DQ2 and DQ8 haplotype, and enteropathy [1]. Currently, the antibodies used for serological diagnostics of celiac disease are antibodies against tissue transglutaminase, deamidated gliadin peptides and the endomysium of the smooth

muscles of the gastrointestinal tract [2]. The basis for a diagnosis of celiac disease is confirmation of histopathological lesions type 2 or 3, according to the Marsh classification as modified by Oberhuber, i.e. crypt hyperplasia, an increased intraepithelial lymphocyte count (over 25 lymphocytes per 100 enterocytes), with or without villous atrophy within the small intestinal mucosa. A biopsy of the small intestine can be skipped only if the patient shows signs indicating celiac disease, has increased

levels of antibodies against tissue transglutaminase (exceeding the norm 10 times), has serum antibodies against the endomysium of the smooth muscles of the gastrointestinal tract and has a genetic predisposition to celiac disease [1].

The few papers published so far indicate that in the majority of patients, the lesions characteristic to celiac disease are located within the mucous membrane of the duodenum and the proximal part of the small intestine [3]. In a small group of patients, focal or continuous lesions may occur in the whole small intestine. Cases have been reported in which villous atrophy and intraepithelial lymphocytosis, characteristic of celiac disease, were identified in biopsy specimens of the mucous membrane of the terminal part of the ileum, taken during ileocolonoscopy [4]. Every tenth celiac disease patient has isolated lesions in the duodenal bulb [5, 6]. A few patients have microscopic and macroscopic lesions in further parts of the small intestine without any abnormalities in the duodenum, which makes it impossible to confirm celiac disease based on biopsy specimens taken from mucous membranes during a traditional gastroduodenoscopy [3].

The so-called endoscopic markers of celiac disease include shortening and thickening of intestinal villi, or a lack of intestinal villi (fissures); flattening or a lack of circular folds; fissures of the mucosa, a mosaic mucosal pattern or granulation of the mucosa [12, 15]. The positive predictive value of endoscopic markers of celiac disease has been assessed at 68%; more specifically, a mosaic structure of the duodenal mucosa has been assessed at 65%, granulation of mucosa at 75.5% and scalloping of circular folds at 64.4% [16]. According to various data, those markers are present in 67–93% patients with celiac disease [15].

The aim of the present study was to assess the presence, range and distribution of macroscopic small intestine lesions in patients newly diagnosed with celiac disease.

Material and Methods

Nine patients aged from 15 to 18 years (average age 16 years) were enrolled in the study, including 7 girls and 2 boys who were diagnosed with celiac disease based on their clinical picture; tests determining the presence of anti-endomysial and/or anti-transglutaminase antibodies and histopathological examinations of biopsy specimens taken from the small intestine.

The levels of serum IgA antibodies were determined in all the patients in the study and were found to be normal in every case. The levels of

serum IgA antibodies against tissue transglutaminase was determined using the ELISA method (Euroimmun Polska, Wrocław) in the Department of Laboratory Diagnostics at the Ludwik Rydygier Collegium Medicum in Bydgoszcz, Poland. A level ≥ 20 RU/mL was considered abnormal. The presence of serum IgA antibodies against endomysium was determined using the indirect immunofluorescence method with monkey esophagus as the antigen (Euroimmun) in the Laboratory of Immunodermatology and Skin Allergic Diseases at the Ludwik Rydygier Collegium Medicum in Bydgoszcz.

For each patient, an endoscopic biopsy of the small intestine was performed and at least 5 mucosa specimens were taken, including 1 taken from the duodenal bulb. The histopathological assessment of the biopsy specimens was performed at the Department of Clinical Pathomorphology using the Marsh classification as modified by Oberhuber. In 8 of the patients, microscopic lesions characteristic of celiac disease were found within the small intestine (3a lesions in 2 patients, 3b lesions in 3 patients, and 3c lesions in 3 patients). In 1 female patient who had antibodies against endomysium, a very high level of antibodies against tissue transglutaminase and a confirmed predisposition to celiac disease (alleles HLA-DQ2 present), no microscopic lesions characteristic to celiac disease were found even after small intestinal endoscopic biopsies were performed twice.

After bowel cleansing using a polyethylene glycol preparation (3–4 liters of Fortrans), all 9 patients underwent an examination of the small intestine using an endoscopic capsule (EndoCapsule EC, Olympus, Tokyo, Japan). The analysis of the endoscopic pictures from all the patients was performed by the same gastroenterologist (A.S-P).

Results

The duration of the capsule's operation was from 4 h 38 min to 9 h 16 min (on average 8 h 4 min). For eight patients the examination of the small intestine was complete. In one case, during 8 h and 54 min of examination, the capsule did not reach the ileocecal valve.

In 6 of the 9 patients examined, the capsule endoscopy picture revealed continuous lesions in the duodenum and the initial part of the small intestine. In 1 child, continuous lesions occurred only in a short section of the bowel, within the duodenum. In 1 patient, the abnormalities revealed by endoscopy were located in the proximal part of the small intestine without any lesions in the duodenum. In 1 case, segmental lesions were observed

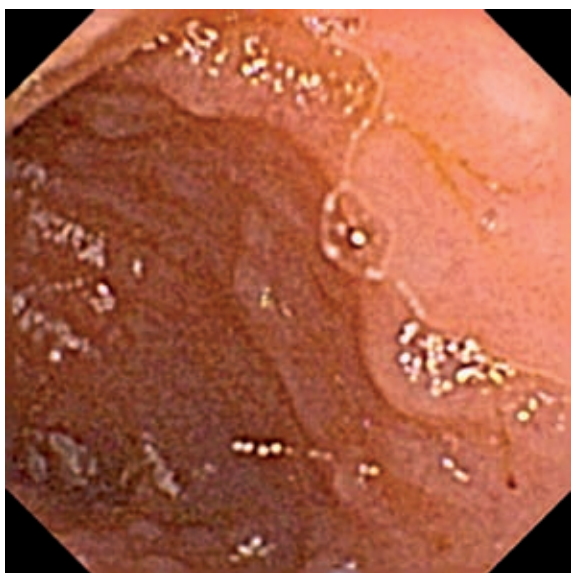


Fig. 1. Granulation and absolute lack of villous structure of the mucous membrane in the small intestine (patient 4)

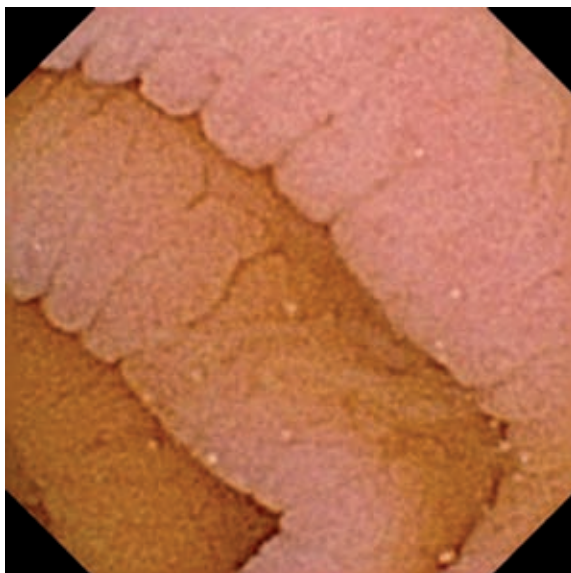


Fig. 2. Fissures of the mucous membrane in the small intestine observed by capsule endoscopy (patient 6)

in the distal part of the small intestine, without any lesions in the duodenum or in the proximal part of the bowel; in that patient, examination of 2 separate mucosa biopsy specimens did not reveal any microscopic lesions characteristic of celiac disease.

The results for the endoscopic markers of celiac disease were as follows: In all patients, significant shortening of villous structure or a complete lack of villous structure was noted; in 6 patients fissures were observed at the peaks of circular folds; in 3 patients there was granulation of the mucosa; in 3 patients there was a mosaic mucosal pattern.

The characteristics of the study group, including the data about the type and range of the lesions in the endoscopic capsule picture, are shown in Table 1.

Discussion

The endoscopic capsule was registered in January 2004 as a small intestinal diagnostic method suitable for children over 10 years old; in the literature; however, there are reports of capsule endoscopy examinations being performed on patients as young as 2–3 years old, and even on infants [7, 8]. The indications for performing capsule endoscopy in children are diverse, and are similar to those for adult patients. They include overt and latent bleeding from the gastrointestinal tract, including bleeding from vascular malformations in the course of Schönlein-Henoch disease, and from Meckel's diverticulum; inflammatory diseases of the small intestine, including Crohn's disease, celiac disease, protein-losing enteropathy, polyps and polyposis syndromes, including Peutz-Jeghers syndrome and familial adenomatous polyposis; and small intestine damage associated with chemotherapy, radiotherapy and graft vs. host disease [8]. The group of pediatric patients who are the most frequently diagnosed using the endoscopic capsule are Crohn's disease patients, in whom the examination is performed in order to diagnose the disease, and to monitor its severity and the efficacy of treatment. These are the reasons for performing 54–86% of pediatric examinations of the small intestine using capsule endoscopy [9, 10].

The value of examinations of the small intestine performed using capsule endoscopy in the diagnosis of celiac disease was confirmed in a meta-analysis published in 2012, based on which the sensitivity of the examination was assessed at 89% and the specificity at 95% [11]. In celiac disease patients capsule endoscopy of the small intestine is recommended in 2 clinical situations.

Capsule endoscopy should be performed in patients for whom gastroduodenoscopy and a small-intestine biopsy is not recommended due to the risk of significant bleeding, e.g. in cases of concomitant purpura; or when gastroduodenoscopy with a small-intestine biopsy cannot be performed due to a lack of consent from the patient or his/her legal guardians; or if, despite strong clinical suspicion of the disease, the lesions characteristic of celiac disease cannot be determined on the basis of biopsy specimens from small intestinal mucosa [12].

Capsule endoscopy should also be offered to patients with celiac disease that is not responding

Table 1. Characteristics of celiac disease patients determined by capsule endoscopy

Number	Gender/ age	Dominant clinical signs	Results of serological tests	Result of small intestine biopsy, according to Marsh	Scope and segmentation of lesions in the small intestine	Type of lesions
1.	M/15 years	abdominal pain	IgATG > 200 RU/mL	3b	duodenum and the initial part of jejunum: continuous lesions	significant shortening of villi
2.	F/15 years	abdominal pain	IgAEmA 1 : 80 IF	3a	duodenum and the initial part of the small intestine: continuous lesions	lack or significant shortening of villi, fissures, granulation, mosaic structure
3.	F/16 years	iron-deficiency anemia	IgAEmA 1 : 160 IF	3b	duodenum: continuous lesions	shortening of villi
4.	F/16 years	abdominal pain	IgATG 129.98 RU/mL	3a	distal part of the small intestine: segmental lesions	significant shortening of villi
5.	F/18 years	iron-deficiency anemia	IgAEmA positive IgATG > 200 Ru/mL	twice M0	proximal part of the small intestine: without lesions; duodenum: continuous lesions	absolute lack of villi, fissures of circular folds, granulation
6.	F/15 years	abdominal pain, chronic diarrhea, iron-deficiency anemia	IgAEmA 1 : 1280 IF	3c	duodenum and the proximal part of the small intestine: continuous lesions	lack of villi, fissures of circular folds, granulation
7.	F/16 years	iron-deficiency anemia	IgAEmA 1 : 640 IF	3b	duodenum and the proximal part of the small intestine: continuous lesions	lack of villi, fissures, mosaic structure
8.	F/16 years	iron-deficiency anemia	IgAEmA 1 : 80 IF	3c	duodenum and the proximal part of the small intestine: continuous lesions	significant shortening of villi, fissures of circular folds
9.	M/17 years	iron-deficiency anemia, short stature	IgATG > 200 RU/mL	3c	duodenum and the proximal part of the small intestine: continuous lesions	villous atrophy, fissures of circular folds, mosaic structure of the mucosa

to dietary treatment (refractory celiac disease). In such patients, using the endoscopic capsule permits severe complications of the disease to be diagnosed, such as ulcerative jejunitis, adenocarcinoma or lymphoma of the small intestine [13, 14].

In the present study, capsule endoscopy of the small intestine was performed in 9 untreated pediatric patients, 8 of whom had a histopathological diagnosis of celiac disease; 1 female patient was diagnosed with celiac disease based on clinical, serological and genetic criteria, but 2 biopsies of the small intestine failed to reveal any microscopic lesions characteristic of celiac disease. The examinations were performed in order to assess the location, distribution and range of lesions determined by endoscopy in the small intestine. To date, such assessments had only been performed in untreated adult celiac disease patients [3].

In the current study, the examinations by capsule endoscopy found lesions in the small intestines of all the patients. This confirms the high sensitivity of this method of examining the small intestine in patients with celiac disease, which has been assessed at 89% on the basis of a meta-analysis of available studies [11].

The present study showed that most pediatric patients with untreated celiac disease have abnormalities determined by endoscopy beginning in the proximal part of the duodenum and stretching continuously into the jejunum or, less frequently, ending in the duodenum. Continuous macroscopic lesions in the duodenum, with or without segmental lesions within the jejunum, were reported by Murray et al. [3] in 91% of adult celiac disease patients in whom capsule endoscopy was performed.

The present study included one very difficult case, from the diagnostic point of view, with lesions determined by endoscopy in the proximal part of the small intestine and no lesions in the duodenum. Lesions with similar localization were observed by Murray et al. [3] in one adult patient with untreated celiac disease. In the present study, this female patient had had a classic gastroduodenoscopy

showing a normal endoscopic picture of the duodenum, and a normal microscopic picture of numerous biopsy specimens of the duodenal mucous membrane, taken during the endoscopy. However, recurring abnormal results of various serological tests, as well as a confirmation of a genetic predisposition in the form of alleles coding HLA DQ2 in the patient with iron deficiency anemia, provided a basis for a diagnosis of celiac disease without confirmation by the small-intestine biopsy. The examination of the small intestine by capsule endoscopy confirmed the incidence of macroscopic (and probably also microscopic) lesions in the jejunum, which are beyond the reach of traditional gastroduodenoscopy.

In the current study, only 1 patient had segmental lesions in the small intestine in the picture obtained by capsule endoscopy. Interestingly, those lesions were found in the further part of the small intestine, and were not accompanied by any visible pathology of the duodenum and the proximal part of the small intestine. In that case, the results of capsule endoscopy only confirmed the diagnosis based on the results of serological and histopathological examinations of biopsy specimens from the mucous membrane of the duodenum, where 3a lesions (according to the Marsh grading system) were found. The low intensity of the microscopic lesions can explain the lack of endoscopic markers of celiac disease. In a study by Murray et al. [3], in 3 out of 38 patients, no abnormalities were found with capsule endoscopy, despite a total lack of villi determined by small intestine biopsy.

The most frequent type of lesion revealed by endoscopy in pediatric patients with untreated celiac disease seems to be continuous lesions in the duodenum and the proximal part of the small intestine. Some patients can develop macroscopic lesions (and probably also microscopic ones) that are beyond the reach of traditional endoscopy. In such cases, capsule endoscopy can help to clearly determine and diagnose celiac disease and to establish the need for lifelong dietary treatment.

References

- [1] Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Philips A, Shamir R, Troncone R, Giersiepen K, Branski D, Catassi C, Lelgeman M, Mäki M, Ribes-Koninckx C, Ventura A, Zimmer KP: ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee; European Society for Pediatric Gastroenterology, Hepatology and Nutrition. European Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr* 2012, 54, 136–160.
- [2] Giersiepen K, Lelgeman M, Stuhldreher N, Ronfani L, Husby S, Koletzko S, Korponay-Szabó IR: ESPGHAN Working Group on Coeliac Disease Diagnosis. Accuracy of diagnostic tests for coeliac disease in children: summary of an evidence report. *J Pediatr Gastroenterol Nutr* 2012, 54, 229–241.
- [3] Murray JA, Rubio-Tapia A, van Dyke CT, Brogan DL, Knipschild MA, Lahr B, Rumalla A, Zinsmeister AR, Gostout CJ: Mucosal atrophy in celiac disease: extent of involvement, correlation with clinical presentation, and response to treatment. *Clin Gastroenterol Hepatol* 2008, 6, 186–193.
- [4] Hopper AD, Huristone DP, Leeds JS, McAlindon ME, Dube AK, Stephenson TJ, Sanders DS: The occurrence of terminal ileal histological abnormalities in patients with coeliac disease. *Dig Liver Dis* 2006, 38, 815–819.

- [5] **Nenna R, Pontone S, Pontone P, Petrarca L, Mennini M, Standoli M, Mastrogiorgio G, Bonamico M, Magliocca FM:** Duodenal bulb in celiac adults: the “whether biopsying” dilemma. *J Clin Gastroenterol* 2012, 46, 302–307.
- [6] **Evans KE, Aziz I, Cross SS, Sahota GR, Hopper AD, Hadjivassiliou M, Sanders DS:** A prospective study of duodenal bulb biopsy in newly diagnosed and established adult coeliac disease. *Am J Gastroenterol* 2011, 106, 1837–1842.
- [7] **Shamir R, Eliakim R:** Capsule endoscopy in pediatric patients. *World J Gastroenterol* 2008, 14, 4152–4155.
- [8] **Jensen MK, Tipnis NA, Bajorunaite R, Sheth MK, Sato TT, Noel RJ:** Capsule endoscopy performed across the pediatric range: indications, incomplete studies, and utility in management of inflammatory bowel disease. *Gastrointestinal Endosc* 2010, 72, 95–102.
- [9] **Cohen SA, Klevens AI:** Use of capsule endoscopy in diagnosis and management of pediatric patients, based on meta-analysis. *Clin Gastroenterol Hepatol* 2011, 9, 490–496.
- [10] **Cohen SA, Ephrath H, Lewis JD, Klevens A, Bergwerk A, Liu S, Patel D, Reed-Knight B, Stallworth A, Wakhisi T, Gold BD:** Pediatric capsule endoscopy: review of the small bowel and patency capsules. *J Pediatr Gastroenterol Nutr* 2012, 54, 409–413.
- [11] **Rokkas T, Niv Y.:** The role of video capsule endoscopy in the diagnosis of celiac disease: a meta-analysis. *Eur J Gastroenterol Hepatol* 2012, 24, 303–308.
- [12] **Chang MS, Rubin M, Lewis SK, Green PH:** Diagnosing celiac disease by video capsule endoscopy (VCE) when esophagogastroduodenoscopy (EGD) and biopsy is unable to provide a diagnosis: a case series. *BMC Gastroenterol* 2012, 12, 90–94.
- [13] **Atlas DS, Rubio-Tapia A, Van Dyke CT, Lahr BD, Murray JA:** Capsule endoscopy in nonresponsive celiac disease. *Gastrointest Endosc* 2011, 74, 1315–1322.
- [14] **Barret M, Malamut G, Rahmi G, Samaha E, Edery J, Verkarre V, Macintyre E, Lenain E, Chatellier G, Cerf-Bensussan N, Cellier C:** Diagnostic yield of capsule endoscopy in refractory celiac disease. *Am J Gastroenterol* 2012, 107, 1546–1553.
- [15] **Akin E, Ersoy O:** Capsule endoscopy in celiac disease. *Gastroenterol Res Pract* 2012, ID 676073.
- [16] **Piazzi L, Zancanella L, Chilovi F, Merighi A, De Vitis I, Feliciangeli G, Borgheresi P, Snider L, Grassi SA, Manfrini C, Orzes N, Bianco MA, Cugia L, Lenoci N, Castagnini A:** Progetto Celiachia-S.I.E.D. Group. Diagnostic value of endoscopic markers for celiac disease in adults: a multicenter prospective Italian study. *Minerva Gastroenterol Dietol* 2008, 54, 335–346.

Address for correspondence:

Anna Szaflarska-Popławska
Department of Pediatric Endoscopy and Gastrointestinal Function Testing
Nicolaus Copernicus University
Szkłodowska-Curie 9
85-094 Bydgoszcz
Poland
Tel.: +48 525 854 850
E-mail: aszaflarska@wp.pl

Conflict of interest: None declared

Received: 18.03.2013

Revised: 8.11.2013

Accepted: 17.09.2014