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ORIGINAL ARTICLE

Association of Intussusception and Celiac Disease in Adults

Tamas A. Gonda · Sharif-Uz-Zaman Khan · Jian Cheng · Suzanne K. Lewis · Moshe Rubin · Peter H. R. Green

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Abstract
Introduction Intussusception (IS) is rare in adults. However, the more frequent use of cross-sectional imaging has resulted in an increase in its detection. Because of the reported association with celiac disease, we determined the prevalence of IS among a cohort with celiac disease.
Methods An anonymized prospectively maintained celiac disease database and radiological database were reviewed.
Results Of a total of 880 patients, 14 (age 47 ± 17.5 years; 50% female) had IS that was detected by CT in 10, capsule endoscopy in three, and barium studies in two. The reason for evaluation was abdominal pain in 78% (11/14), whereas in the remainder (3/14) were incidental. IS was the initial manifestation of celiac disease in 57% (8/14). Two patients were found to have lead-point intussusceptions and both had small-bowel adenocarcinoma, and 10/14 had severe villous atrophy (subtotal or total). Among those with established celiac disease, IS was detected early, within 3 years of diagnosis. Follow-up was available for 11 patients, 9 of who adhered strictly to a gluten-free diet, and six had no recurrence. Among all the patients diagnosed with IS on radiologic studies at our institution, 45 were considered to have idiopathic IS. Only two of these patients had evaluation for celiac disease.
Conclusion IS occurs in celiac disease. It may be the initial presentation and is associated with abdominal pain. Adenocarcinoma needs to be excluded. The majority of patients do not have recurrent symptoms after adherence to a gluten-free diet. Celiac disease should be considered more frequently when IS is encountered.

Keywords Celiac disease · Intussusception · Abdominal pain

T. A. Gonda · S. Khan · J. Cheng · S. K. Lewis · M. Rubin · P. H. R. Green (✉)
Division of Digestive and Liver Diseases, Department of Medicine, Celiac Disease Center, Columbia University Medical Center, New York, NY, USA
e-mail: pg11@columbia.edu

T. A. Gonda
e-mail: tg2214@columbia.edu

M. Rubin
Division of Gastroenterology,
New York Hospital Queens, New York, NY, USA

Introduction

Intussusception, a method of telescoping of one bowel loop into an adjacent one, is the most common cause of small-bowel obstruction in children under the age of five. A structural lesion or lead point is only identified in 5–15% of cases, and the majority of cases (>80%) resolve with conservative management [1, 2]. In contrast, adult intussusception is uncommon (approximately 5% of all cases) and is thought to be due to structural lesions in over 80–90% of cases in retrospective series of surgical cases [3–7]. While this data has been supported by retrospective reviews in the surgical literature, more recent reviews of intussusception identified on imaging studies found that only 30% of patients had an identifiable lead point, and that over 50% of patients without an identifiable lead point had "idiopathic" intussusception [8–11]. The majority of adult cases, both in surgical series [4–7] and in the radiologic literature [3, 9, 11, 12], were entero-enteric or ileo-colic intussusceptions, and the majority of non-neoplastic cases were entero-enteric. While the majority of non-lead entero-enteric intussusceptions were categorized as idiopathic in

these series, the evaluation and follow-up in these cases was not extensive. Reported causes of entero-enteric non-lead point intussusceptions are inflammatory processes (adjacent pancreatitis, cholecystitis, appendicitis), adhesions, celiac disease, Crohn's disease, scleroderma, and cystic fibrosis [3].

Among these diagnoses, celiac disease stands out as one that is least likely to be associated with other clinical findings at the time of diagnosis of intussusception. There are several case reports, both in the adult and in the pediatric literature of intussusception as the presenting sign of celiac disease [8, 13–15]. On the other hand, prospective studies of patients (both symptomatic and asymptomatic at the time) with celiac disease who underwent MRI and CT studies found that four out of 31 and six out of 28 patients had incidentally found intussusceptions [16, 17]. In countries where ultrasound is commonly used for the evaluation of intestinal diseases, "intermittent invaginations" were seen in 30% of a series of patients with celiac disease [18]. Among celiac disease patients undergoing capsule endoscopy in a series of 48 patients, one case of intussusception was identified [19].

The latter imaging studies suggest that intussusception may be common in celiac disease. We therefore studied the prevalence of intussusception in our cohort of patients with celiac disease, and characterized their presentation, clinical features, and outcome.

Methods

We reviewed an anonymized database of patients with celiac disease seen at the Celiac Disease Center at the Columbia University Medical Center between 1981 and 2006. Clinical data was entered into the database retrospectively for those seen prior to 1990 and prospectively since this time. The database consisted of 880 patients with a biopsy-proven diagnosis of celiac disease. We have searched this database for all patients who have undergone imaging studies (CT or MRI of the abdomen, video capsule endoscopy (VCE), or small-bowel series (SBS)). Among these patients, we identified those who were diagnosed with intussusception on any of these examinations. We determined the initial manifestations and severity of the disease, the indication for imaging studies, and evaluation for other possible etiologies of IS.

In addition, we also conducted a database search of all radiologic studies performed at our institution to determine the prevalence of IS in our institution. We have divided these patients into two groups: IS with a known cause (where a final pathologic diagnosis was made) and idiopathic IS. We reviewed the medical records of patients with "idiopathic IS" for evidence of further diagnostic testing (endoscopic duodenal biopsies, basic laboratory tests and tissue-transglutaminase, anti-gliadin or anti-endomysial antibodies) that may suggest or be associated with CD.

Statistical analysis using Pearson's Chi-square test for categorical data and Student's *t*-test for two-sample continuous variables was performed comparing the baseline demographic characteristics of patients with celiac disease and intussusceptions to all celiac disease patients in the database.

Results

Diagnosis of Intussusception in Patients with Celiac Disease

Of 880 patients in the database with biopsy-proven celiac disease, we identified 225 who had undergone a total of 313 imaging studies for any indication between 1981 and 2005. Of these 225 patients, 14 were identified to have imaging evidence of IS (Table 1). All cases identified with IS occurred after 1998, which may correspond to the increasing use of cross-sectional imaging in the evaluation of these patients. The total number of cases diagnosed in our database after this date was 612. The majority of individuals with an IS ($n = 10$) were detected on CT whereas three patients were found to have IS on VCE and one on a small-bowel barium study. One patient had evidence of IS on two imaging modalities, and two patients had recurrent IS.

The average age of the patients was 47 ± 16.9, with a M/F ratio of 1/1, which was not significantly different from the average age (42.7 ± 17.9) and sex distribution (1/2.1) of all patients in our database.

Presentation of Intussusception

Overall, 80% (11/14) of the patients who presented with intussusception had abdominal pain. The majority, (9/14) were diagnosed with intussusception either prior to or at the time of the diagnosis of celiac disease. In two patients the intussusception was incidental. Both of these patients had non-lead point intussusception. One of these patients underwent CT scan for follow-up of testicular cancer treatment and was incidentally noted to have intussusception. A VCE subsequently showed significant scalloping and an endoscopy and duodenal biopsies confirmed celiac disease. The other patient with incidental intussusception initially underwent endoscopy for the work-up of diarrhea and weight loss and was found to have biopsies and serologies consistent with celiac disease. He subsequently underwent VCE to evaluate the extent of small-bowel disease. VCE identified villous abnormalities in the duodenum and an intussusception in the distal jejunum.

Table 1 Presentation and diagnosis of intussusception in patients with celiac disease

	Number of patients ($n = 14$)
Time interval between diagnosis of CD and IS (years)	0.97 ± 1.6
Presenting symptom of IS	
Abdominal pain	11/14 (78%)
Incidental finding	3/14 (22%)
Diagnostic study	
CT	10 (71%)
SBFT	3 (21%)
VCE	2 (15%)
Lead point IS	2 (15%)[a]
Non-lead point IS	12 (85%)
History of abdominal surgery	4 (28%)
Site of IS	
Jejunum	8 (56%)
Ileum	6 (44%)

IS intussusceptions, *CD* celiac disease

[a] Both of these cases were identified to have small-bowel adenocarcinoma

In seven patients, the diagnosis of an intussusception led to the diagnosis of celiac disease (of note, five of these patients underwent diagnostic imaging at another medical facility). While these patients were found to have other manifestations of celiac disease (anemia, vitamin deficiencies, osteopenia), none were aware of these conditions prior to the diagnosis of intussusception, or had diarrhea. Two of these patients were identified to have a lead point and both were diagnosed with small-bowel adenocarcinoma. Histological evidence of celiac disease was found in the resected, adjacent small-bowel mucosa and confirmed by duodenal biopsy. The other five patients had no lead point. Three of these patients had previous surgery. No other risk factors for intussusception were found.

In five patients, intussusception was diagnosed 6 months to 5 years after the diagnosis of celiac disease. Four of them underwent CT and VCE for work-up of recurrent abdominal pain, and one patient VCE was performed for the evaluation of occult gastrointestinal bleeding. This patient did not have associated pain. None of these five patients had lead point intussusception.

Severity of Celiac Disease in Patients with Intussusceptions

The majority of patients (72%) had a more severe degree of villous atrophy, though this was not significantly different from the entire cohort (49%) (Table 2). The distribution of severity of pathologic changes showed a trend towards more severe disease at diagnosis compared to the entire database but this difference was not significant ($p = 0.07$). All patients who had serologic testing had positive anti tissue-transglutaminase antibodies or anti-endomysial antibodies. Among the comorbidities, one patient was identified with endometriosis and another with microscopic colitis that may have contributed to intra-peritoneal inflammations or adhesions as risk factors for intussusception.

Table 2 Presentation and severity of celiac disease in patients with intussusception

	CD and IS ($n = 14$)	All CD patients ($n = 880$)
Sex (M/F)	1/1	1/2.1
Average age at presentation	47 ± 16.9	42.7 + 17.9
Marsh–Oberhuber 3b–3c	72%	49.3%
Marsh–Oberhuber 3a	21%	49.3%
Marsh–Oberhuber 1–2	7%	1.4%

None of these differences were significant between the groups. Marsh–Oberhuber 3b–3c: moderate to severe villous atrophy, crypt hyperplasia and increased intraepithelial lymphocytes (IELs); Marsh–Oberhuber class 3a: mild villous atrophy, crypt hyperplasia and IELs; Marsh 1–2: presence of increased IELs with or without crypt hyperplasia and without villous atrophy

Course of Disease

Follow-up information was available for 11 patients at a mean of 3.4 ± 1.5 years (Table 3). Five patients reported recurrence of pain and three of these patients were found to have recurrence of intussusception on further imaging. Of the 11 patients with symptomatic intussusception, nine patients were documented to be adherent to a GFD, five had no recurrence of symptoms, whereas four remained symptomatic with recurrent abdominal pain. Of the five patients with resolved symptoms, three had repeat biopsies and these showed significant histological improvement. One patient, not strictly adherent to the diet had recurrent episodes of pain, documented intussusception and several laparoscopies as management of the pain and intussusception.

Diagnostic Approach to Intussusceptions in the General Population

Given the possibility that IS is an increasingly frequent diagnosis in adults, we were interested to understand the approach to the management of patients diagnosed with IS at our institution. Among over 1.7 million radiologic studies performed at our institution between 01/01/2001 and 12/31/2005, 204 patients were diagnosed with intussusceptions on CT or MRI or small-bowel series and 45/204 were idiopathic (a final pathologic diagnosis was

Table 3 Follow-up of patients with celiac disease and intussusception

Case	Histologic classification at diagnosis	Follow-up (years)	Histologic classification at follow-up	Adherence to GFD	Recurrence of symptoms	Recurrence of IS
A	3b	3	3a	−	+	+
B	3b	3	n/a	−	−	−
C	3c	2	3b	+	−	−
D	3c	2	n/a	+	+	−
E	3a	7	2	+	−	−
F	3c	4	n/a[a]	+	−	−
G	3b	3	0	+	+	+
H	3c	2	2	+	−	−
I	3c	4	n/a	+	−	−
M	3c	5	3a	+	+	+
N	3b	2.5	n/a	+	+	−

[a] While follow-up biopsies were not obtained, video capsule endoscopy showed no evidence of changes suggestive of celiac disease 3 years after diagnosis

not made as an etiology of IS). Among these patients, 5/45 underwent upper endoscopy and 2/45 (both included in the cohort) had biopsy-proven celiac disease. In addition, we have examined the prevalence in this series of anemia (Hb <12 in women ($n = 27$) and <13 in men ($n = 26$)) (22/45); iron deficiency (6/45); Vitamin B12 deficiency (0/45) osteopenia or osteoporosis (1/45). We reviewed the chart of patients with anemia, not otherwise specified, iron deficiency and b12 deficiency and osteopenia or osteoporosis. None of these patients had antibody testing or endoscopic biopsies performed. A potential limitation of this retrospective chart review is that we were unable to obtain records other than those that were performed at our institution. These data suggest that while a substantial number of intussusceptions cases are idiopathic, celiac disease is not considered as an etiology. Several of these patients manifest possible complications of celiac disease and may have other reasons that warrant further testing. These findings underline the importance that the diagnosis of intussusceptions should prompt an evaluation for celiac disease.

Discussion

Intussusception is being diagnosed with increasing frequency in adults and it is expected that a majority of these cases will no longer be associated with a lead point [11]. Non-lead point intussusception has often been categorized as idiopathic and this group of patients may have unrecognized small-bowel disease, such as inflammatory (inflammatory bowel disease, eosinophilic enteritis, or celiac disease) or infectious diseases. An association between celiac disease and idiopathic intussusception has been demonstrated by previous case reports and series [20, 21]. Both inflammation and decreased small-bowel motility has been proposed as an etiology of intussusception in celiac disease [22]. Our study provides the largest review to date of intussusception in adult patients with celiac disease. Intussusception in those undergoing abdominal imaging is more common among patients with celiac disease (1.6%) than in the general population undergoing abdominal scanning (0.2%) [7].

Perhaps the most important finding of this study is that intussusception may be the initial manifestation of celiac disease. The majority of our cases (78%) were non-lead point intussusceptions, and this underlines the importance of a complete evaluation at the time of diagnosis of "idiopathic" intussusception in adults.

Although the majority of cases in this review are non-lead point intussusceptions the two cases of lead point intussusception in the context of previously unrecognized celiac disease were caused by small-bowel adenocarcinoma. Because both adenocarcinoma and lymphoma of the small intestine occur at an increased frequency in celiac disease, our observation further emphasizes the role of an evaluation of intussusception associated with celiac disease to rule out associated malignancy [20, 23]. Other studies have also shown that IS in established patients with celiac disease is more commonly seen in type II refractory celiac disease [24].

Our retrospective review of cases of IS, diagnosed radiologically, over a 5-year period at our institution and the low frequency of testing for celiac disease further underlines that celiac disease may be a significantly under-recognized etiology of intussusception.

The majority of patients with celiac disease in whom IS was detected had abdominal pain. Recent studies have demonstrated that celiac disease is associated with acute abdominal pain. In a case-controlled study of patients presenting to an emergency room, Sanders et al. [21] found that 3% had celiac disease. This figure rose to 10.5% in

those with non-surgical abdominal pain. While the findings of imaging studies were not reported by these authors, it is probable that some of these patients may have had intussusception.

The observation that intussusception can be observed in those with celiac disease who are undergoing evaluation with CT scan, abdominal ultrasound, or VCE, suggests that these patients may undergo spontaneous intussusception relatively frequently. However, IS does appear to be associated with the occurrence of abdominal pain, and the presence of more severe degrees of villous atrophy.

In conclusion, we found intussusception to be relatively common among patients with celiac disease. Idiopathic intussusception should prompt an evaluation for celiac disease, and intussusception should also be suspected in patients with known celiac disease presenting with abdominal pain.

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