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There might be a distinctive clinical phenotype of constipation with non-cardiac chest pain which responds to combination laxatives

A retrospective, longitudinal symptom analysis

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Abstract

Proton pump inhibitor (PPI)-refractory non-cardiac chest pain (NCCP) is often resolved when constipation was relieved. This study aimed to investigate the clinical features of patients with both NCCP and constipated functional bowel disorders (FBD).

Among 692 consecutive patients diagnosed with functional constipation or irritable bowel syndrome with constipation and underwent anorectal manometry (ARM) in our hospital, PPI-refractory NCCP was present in 37. The clinical course of various torso symptoms including NCCP and ARM findings were retrospectively evaluated.

The mean age was lower in the NCCP than in the non-NCCP group (57.4 vs 61.3 years, respectively, $P = .042$). Back pain (16.2% vs 2.0%, $P < .001$) and sharp abdominal pain (13.5% vs 0.9%, $P < .001$) were more common in the NCCP group. Increased resting pressure (16.2% vs 6.9%, $P = .036$) and squeezing pressure (62.2% vs 50.7%, $P = .049$) of the anal sphincter, increased urgency volume (40.5% vs 23.2%, $P = .004$), and maximal volume (25.7% vs 15.0%, $P = .032$) for rectal sensation were more frequently observed in the NCCP group. After taking laxatives for 1 to 3 months, 81.1% of patients with NCCP reported improvement.

Subjects with NCCP showed decreased rectal sensation more frequently at anorectal manometry. Majority of patients with NCCP reported improvement of symptom upon relief of constipation. Constipation might be a therapeutic target in patients with NCCP related to constipated functional bowel disorders.

Abbreviations: ARM = anorectal manometry, EGD = esophagogastroduodenoscopy, FBD = functional bowel disorders, FDD = functional defecation disorder, FGID = functional gastrointestinal disorders, GERD = gastroesophageal reflux disease, GI = gastrointestinal, IBS = irritable bowel syndrome, IBS-C = irritable bowel syndrome with constipation, NCCP = non-cardiac chest pain, PPI = proton pump inhibitor, SD = standard deviation.

Keywords: anorectal manometry, constipation, functional bowel disorder, noncardiac chest pain

1. Introduction

Non-cardiac chest pain (NCCP) is defined as recurrent angina-like retrosternal chest pain of non-cardiac origin. According to some studies investigating the epidemiology of NCCP in different populations, the prevalence of NCCP was 13.9% to 33%.[1–3] Even after having serious cardiac diseases was ruled out, the patients diagnosed with NCCP often lead restricted lifestyles, believing they have undiscovered heart diseases.[4,5] They also frequently seek healthcare services, which results in an increased individual and nationwide cost burden.[6]

Patients with NCCP are often referred to clinics in departments of gastroenterology after undergoing a thorough evaluation in the department of cardiology or pulmonology seeking an organic cause of the chest pain in the upper torso. After thorough evaluation, many of them are diagnosed with gastroesophageal reflux disease (GERD), which is the leading known cause of NCCP.[7,8] Although proton pump inhibitor (PPI) is the treatment of choice for patients with GERD, 10% to 40% of these patients fail to show a symptomatic response to standard-dose PPI therapy.[9] This group of patients is identified as having refractory GERD.

A concomitant functional bowel disorder and visceral hypersensitivity are included in several putative mechanisms of

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refractory GERD.[10] While the mechanism of NCCP is still not fully understood, underlying causes of GERD-unrelated NCCP are mainly thought to be of esophageal origin.[11] This category includes esophageal motility disorders and functional chest pain of presumed esophageal origin according to ROME III criteria.[12] However, since esophageal motility disorders are quite rare diseases that usually present with dysphagia, they can be excluded by a review of the accompanied symptoms.[13] Still, some patients who are not classified into aforementioned categories and unresponsive to PPI or pain medications are afflicted with persistent NCCP. Among the patients referred to the Functional Gastrointestinal Disorders (FGID) Clinic due to constipation and/or various torso symptoms of unknown origin, we found that some were also suffering from NCCP. In the follow-up visits at 1 to 3 months, after empirical treatments for constipation, many of the patients reported that the chest pain was resolved once the constipation was relieved.

To explain this observation, we reviewed the relevant literature. In one previous study, when the lumen of the gastrointestinal (GI) tract was distended by a pneumatic balloon, referred pain occurred in various areas.[14] This finding indicated that referral pain in the epigastric area may not necessarily have been caused by problems in the esophagus but could have been caused by problems in the more distal portion of the gut. Moreover, it could be inferred that constipation may cause referral pains in various parts of the torso, including NCCP, since constipation is a major pathophysiological cause of solid-, fluid-, or gas-induced distension of the gut.

We hypothesized that if constipation could cause NCCP, there might be some distinctive clinical features in patients with both NCCP and constipated functional bowel disorder (FBD) which could help distinguishing the origin of NCCP and choosing the treatment modality in these patients. Here we aimed to investigate the differences in constipated patients by NCCP status and determine whether NCCP resolves after treatment for constipation.

2. Materials and methods

2.1. Patients and diagnostic criteria

This retrospective observational study included a longitudinal symptom analysis. Among the patients referred to the FGID clinic of our hospital, those who were diagnosed with either functional constipation, irritable bowel syndrome with constipation (IBS-C), or functional defecation disorder (FDD) compatible to Rome III criteria and underwent ARM due to suspicious dyssynergic defecation between December 2012 to August 2015 were included. On the first visit to the clinic, patients were encouraged to report any present symptom through an open question. Every symptom reported by the patient was recorded. During the follow-up period, the clinical course of each symptom was evaluated by specifically questioning if it worsened, improved, or remained unchanged since the laxatives had been prescribed. Medical records of the included patients were retrospectively reviewed. The definition of NCCP was recurrent episodes of retrosternal chest pain, which is not of cardiac origin, and also not from GERD or organic upper GI diseases. The possibility of chest pain from cardiac origin had been excluded in the thorough evaluation performed in the department of cardiology or emergency medicine. The association between chest pain and exercise was always questioned, and further cardiac evaluations included electrocardiography, echocardiography, coronary computed tomography angiography, exercise stress testing, and coronary angiography. Afterwards, these patients underwent EGD evaluation and received empirical standard-dose PPI therapy for at least 4 weeks to exclude the possibility of chest pain of structural upper-GI origin or GERD. Because our center was a tertiary referral center, many of the patients with chest pain had already underwent standard dose PPI trial of more than 4 weeks in the primary or secondary care centers. If PPI trial had not been performed before the visit to our center, 4 weeks of standard dose PPI was prescribed to those patients with chest pain after cardiac evaluation. Only those without improvement of chest pain despite the PPI therapy in our center or previous medical centers, and not having any abnormal EGD findings that could explain the symptom were included in the NCCP group. In some patients complaining of epigastric fullness which could be confused with dysphagia, esophageal manometry was performed to exclude esophageal motility disorders. The patients with NCCP were assigned to the NCCP group, while the rest were assigned to the non-NCCP group.

This study was approved by the Seoul National University Hospital Institutional Review Board (Decision date: 18 January 2016, IRB number: H-1601–030-733) and conducted in accordance with the *Declaration of Helsinki*. Patient consent was waived, given the retrospective nature of this study.

2.2. Target symptoms and definition

Data regarding baseline characteristics such as age and sex were collected. A variety of torso symptoms reported by the patients were reviewed, including epigastric fullness, nausea, vomiting, bloating, dull abdominal pain, sharp abdominal pain, back pain, flank pain, flatulence, and anal pain. Sharp abdominal pain was of a throbbing or pricking nature. Back pain was mainly of a throbbing nature in the upper back area. Data obtained from ARM were also analyzed.

2.3. Anorectal manometry

ARM was performed in every included patient to assess various anorectal pressure correlations. Assessed items included anal sphincter tone, resting and squeezing anal sphincter pressure, sustained squeezing time of the anal sphincter, the rectoanal inhibitory reflex, the coughing reflex, rectal volume measurement, and the balloon expulsion test. The methods for conducting and analyzing ARM are detailed elsewhere (see Text, Supplemental Content, http://links.lww.com/MD/D37, which shows the detailed protocol of conducting and analyzing ARM).

2.4. Treatment and response evaluation

After evaluation, only combination laxatives (bulk forming agents and osmotic laxatives) were prescribed first to the patients in the NCCP group as well as the non-NCCP group. At this time, as chest pain was not responsive to PPI therapy, PPI was not prescribed. The regimen was comprised of Agiocur granule (Plantago seed 3.9 g, Ispaghula husk 0.132 g per 6 g sachet) 12 to 18 g/day, 50% lactulose syrup 30 to 45 mL/day, magnesium oxide 1 to 1.5 g/day. The response to laxatives was judged by symptom improvements reported by the patients during follow-up visits to the outpatient clinic. For the patients with NCCP, the

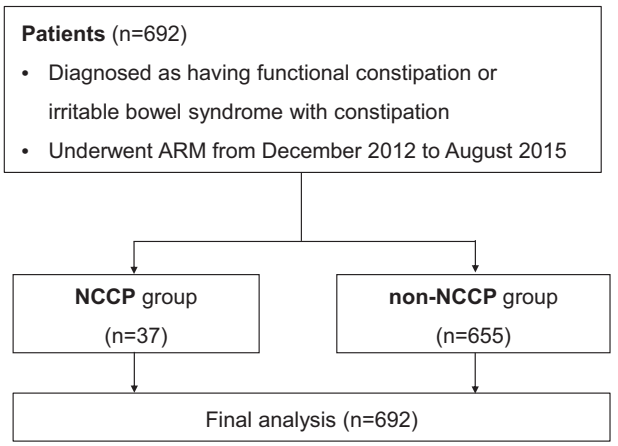

Figure 1. Overview of the patient selection process. ARM = anorectal manometry, NCCP = non-cardiac chest pain.

frequency and intensity of pain were evaluated at every visit. The change of NCCP was assessed as 'worsened', 'no change' or 'improved'. If there is an improvement in either the frequency or intensity of NCCP without aggravation of the other, the response to laxatives was regarded as 'improved'. For the rest of NCCP patients who did not respond to laxatives, prescription of pain modulators such as tricyclic antidepressants, serotonin uptake inhibitors or serotonin-norepinephrine reuptake inhibitors were considered. Patients were followed regularly afterward through the FGID clinic of our hospital.

2.5. Statistical analysis

Continuous variables were analyzed using Student *t* test, while categorical variables were analyzed using the $\chi 2$ method or Fisher exact test. Categorical variables were analyzed using a linear by linear association test. To adjust for the effect of age on ARM findings, a subgroup analysis was conducted of patients < 60 years vs those ≥ 60 years. Results of $P < .05$ were considered statistically significant. IBM SPSS statistics version 21 was used for all of the statistical analyses.

3. Results

3.1. Patient characteristics

A total of 692 constipated patients (37 in the NCCP group, 655 in the non-NCCP group) met the inclusion criteria (Fig. 1). This patient population comprised 203 patients with IBS-C, 186 patients with functional constipation, and 303 patients with functional FBD. The mean patient age was 57.4 ± 12.0 for the NCCP group and 61.3 ± 14.6 for the non-NCCP group ($P = .042$) (Table 1). The proportions

Table 1

Baseline characteristics of the total population (n = 692).

Variables	NCCP (n = 37)	Without NCCP (n = 655)	*P* value
Mean age ± SD, years	57.4 ± 12.0	61.3 ± 14.6	.042*
Gender, male	13 (35.1)	246 (37.6)	.767†
GI symptoms			
Epigastric fullness	3 (8.1)	25 (3.8)	.184‡
Nausea/vomiting	5 (13.5)	67 (10.2)	.576‡
Bloating	19 (51.4)	251 (38.3)	.114†
Dull abdominal pain	10 (27.0)	162 (24.7)	.753†
Sharp abdominal pain	5 (13.5)	6 (0.9)	<.001‡
Back pain	6 (16.2)	13 (2.0)	<.001‡
Flank pain	0	18 (2.7)	.617‡
Flatulence	1 (2.7)	18 (2.7)	1.00†
Anal pain	2 (5.4)	54 (8.2)	.76†
Anorectal manometry			
Anal tone	2/33/2	105/424/79	.040†
Decreased / Normal / Increased	(5.4/89.2/5.4)	(17.3/69.7/13.0)	
Anal sphincter, resting pressure	14/17/6	332/278/45	.036§
Decreased / Normal / Increased	(37.8/45.9/16.2)	(50.7/42.4/6.9)	
Anal sphincter, squeezing pressure	0/14/23	70/253/332	.049§
Decreased / Normal / Increased	(0/37.8/62.2)	(10.7/38.6/50.7)	
Decreased sphincter duration	22 (59.5)	313 (47.8)	.167†
Positive RAIR	35 (94.6)	579 (95.1)	.704‡
Positive coughing reflex	35 (94.6)	516 (84.3)	.090†
Rectal sensation, minimal volume	0/16/20	43/292/317	.194§
Decreased / Normal / Increased	(0/44.4/55.6)	(6.6/44.8/48.6)	
Rectal sensation, urgency volume	2/20/15	132/368/151	.004§
Decreased / Normal / Increased	(5.4/54.1/40.5)	(20.3/56.5/23.2)	
Rectal sensation, maximal volume	9/17/9	262/278/95	.032§
Decreased / Normal / Increased	(25.7/48.6/25.7)	(41.3/43.8/15.0)	
Rectal compliance	16/6/7	352/85/132	.632§
Decreased / Normal / Increased	(55.2/20.7/24.1)	(61.9/14.9/23.2)	
Failed balloon expulsion test	18 (48.6)	375 (61.7)	.115†
Bearing down rectal pressure	2/7/27	30/170/409	.467§
Decreased / Insufficient elevated / Normal	(75.0/19.4/5.6)	(4.9/27.9/67.2)	
Bearing down anal sphincter pressure	7/11/19	96/147/367	.346§
Normal / Incomplete relaxation / Paradoxical contraction	(18.9/29.7/51.4)	(15.7/24.1/60.2)	
Mean follow-up duration ± SD, months	9.9 ± 11.2	9.6 ± 13.5	

Values are number (%) unless stated otherwise.

GI = gastrointestinal, NCCP = non-cardiac chest pain, RAIR = rectoanal inhibitory reflex, SD = standard deviation.

* Student's *t* test.

† Chi-square test.

‡ Fisher exact test.

§ Linear by linear association.

of male sex were 35.1% in the NCCP group and 37.6% in the non-NCCP group. Among the symptoms reviewed, bloating was most frequently observed, followed by dull abdominal pain and nausea as well as vomiting in both groups. Epigastric fullness, flank pain, flatulence, and anal pain were observed at frequencies of less than 10% in both groups.

3.2. Association of GI symptoms and ARM findings with NCCP

Two of the GI symptoms were significantly associated with NCCP (Table 1). Sharp abdominal pain was observed more frequently in the NCCP group (13.5%, 5 of 37) than in the non-NCCP group (0.9%, 6 of 655) ($P < .001$). Back pain was also observed more frequently in the NCCP group (16.2%, 6 of 37) than in the non-NCCP group (2.0%, 13 of 655) ($P < .001$). Among the ARM findings, anal tone, resting and squeezing pressure of the anal sphincter, urgency, and maximal volume for rectal sensation differed significantly between groups (Table 1). Fewer patients in the NCCP group than in the non-NCCP group showed abnormal anal tone (10.8% vs 30.3%, $P = .011$). On the other hand, a higher proportion of patients in the NCCP group had increased resting pressure (16.2% vs 6.9%, $P = .036$) and squeezing pressure (62.2% vs 50.7%, $P = .049$) of the anal sphincter. More patients were observed to have increased urgency volume (40.5% vs 23.2%, $P = .004$) and increased maximal volume (25.7% vs 15.0%, $P = .032$) for rectal sensation in the NCCP group than in the non-NCCP group.

3.3. Age-stratified analysis

In subgroup analyses according to age which could have a substantial influence on ARM finding, patients < 60 years and those ≥ 60 years showed similar associations with NCCP in both GI symptoms and ARM findings (Table 2). In patients < 60 years, sharp abdominal pain (15.0% vs 0.4%, $P = .001$) and back pain (20.0% vs 2.5%, $P = .004$) were more common in the NCCP group than in the non-NCCP group, respectively. More patients in the NCCP group had an increased urgency volume for rectal sensation ($P = .034$). In patients ≥ 60 years, sharp abdominal pain (11.8% vs 1.3%, $P = .032$) and back pain (11.8% vs 1.6%, $P = .042$) were also more common in the NCCP group. While more patients in the NCCP group tended to have an increased urgency volume for rectal sensation, the statistical significance was equivocal ($P = .050$).

3.4. Response to laxatives

Laxatives were prescribed to all 37 patients with NCCP; of them, 30 patients (81.1%) reported improvement of NCCP upon constipation relief. Interestingly, a substantial proportion of patients in the NCCP group reported a decreased incidence of chest pain attacks even before improvement of constipation. The proportions of patients with improvement of NCCP were not significantly different between the patients with FBD (functional constipation or IBS-C) and the patients with FDD (77.8% vs 84.2%, $P = .693$). The mean follow-up duration was 9.9 ± 11.2 months in the NCCP group versus 9.6 ± 13.5 months in the non-NCCP group.

4. Discussion

In this study conducted in constipated FBD patients, there were several differences in the clinical findings among the patients with NCCP and those without NCCP. Sharp abdominal pain and back pain were more frequently observed in patients with NCCP regardless of age. The ARM findings demonstrated that fewer patients in the NCCP group had decreased anal tone as well as decreased resting and squeezing pressure of the anal sphincter. In addition, urgency volume for rectal sensation was increased in higher proportions of subjects with NCCP, which was uniformly observed in age-stratified subgroup analyses. After the laxative treatment for 1 to 3 months, the majority of patients with NCCP (81%) reported improvement of NCCP symptom as well as constipation.

Reportedly, there is considerable overlap between upper- and lower-GI symptoms in IBS, and IBS-C accompanies bloating and upper or lower abdominal symptoms more frequently than IBS with diarrhea.[15] However, the pathophysiology underlying the frequent coexistence of upper- and lower-GI symptoms in IBS-C patients is still unclear. There have been many attempts to elucidate the origin of various upper GI symptoms in constipated patients. To date, esophageal problems are frequently considered the main cause of NCCP. Many current studies reported functional chest pain being of esophageal origin even after excluding GERD and esophageal motility disorders.[16–18]

Table 2

Age specific association of symptoms and anorectal manometry findings with non-cardiac chest pain.

	Subjects younger than 60			Subjects of 60 or older		
Variables	**NCCP (n = 20)**	**Without NCCP (n = 275)**	***P* value**	**NCCP (n = 17)**	**Without NCCP (n = 380)**	***P* value**
Mean age ± SD, years	48.6 ± 8.6	47.4 ± 10.5	.608*	67.8 ± 4.7	71.4 ± 6.6	.026*
Gender, male	4 (20.0)	92 (33.5)	.215†	9 (52.9)	154 (40.5)	.309†
GI symptoms						
Sharp abdominal pain	3 (15.0)	1 (0.4)	.004‡	2 (11.8)	5 (1.3)	.032‡
Back pain	4 (20.0)	7 (2.5)	.004‡	2 (11.8)	6 (1.6)	.042‡
Anorectal manometry						
Rectal sensation, urgency volume	2/9/9	51/162/60	.034§	0/11/6	81/206/91	.050§
Decreased / Normal / Increased	(10.0/45.0/45.0)	(18.7/59.3/22.0)		(0/64.7/35.3)	(21.4/54.5/24.1)	

Values are number (%) unless stated otherwise.

GI = gastrointestinal, NCCP = non-cardiac chest pain, SD = standard deviation.

* Student's *t* test.

† Chi-square test.

‡ Fisher exact test.

§ Linear by linear association.

However, evidence shows that functional chest pain may not be entirely of esophageal origin. In one study, patients with functional chest pain did not show significant differences in response to electrical stimulation of the esophagus.[19] In another study comparing the psychophysiological profiles between patients with functional chest pain and healthy subjects, significant intergroup differences in sympathetic and parasympathetic tone were observed.[20] These findings, together with those of the present study, indicate that causes of NCCP of origins other than esophagus should be further investigated.

Among the analyzed GI symptoms, dull abdominal pain could be presumed to represent visceral pain, whereas sharp abdominal pain, back pain, and NCCP had a throbbing or pricking nature and were specifically locatable in most patients. These symptoms seem to be somatic referral pains according to pain nature and location. Therefore, the result can be interpreted as NCCP in patients with constipated FBD being one of somatic referral symptoms from the gut rather than visceral pain per se. In addition, the ARM findings of overall higher pressure of the anal sphincter and more frequently decreased rectal sensation in the NCCP group support that there might be a distinctive pathophysiology in the development of constipation as well as NCCP in some patients with dyssynergic defecation. In patients with constipation, the gut could frequently become distended with gas, fluid, and solid materials. Higher pressure exerted by the anal sphincter might result in higher intraluminal pressure and cause noxious sensory signals in the gut.

Like other visceral organs, the gut does not include nociceptors, the pain receptors in the somatic sensory system that are responsible for the somatic pains we perceive. Rather, sensory perceptions in the gut depend on mechanoreceptors, chemoreceptors, and tension receptors.[21,22] Thus, acquired neural stimuli are integrated in the enteric nervous system and generate propulsive movement. Likewise, the enteric nervous system is modulated by the autonomic nervous system.[22] It has not been clearly elucidated, however, whether these enteric signals can be conducted to the splanchnic nerves and, in turn, to the spinal cord to generate "somatic referral pain." Since such conduction is not usually manifested, it can be termed aberrant projections. In a study of children with functional bowel disease, upper abdominal pain in areas as high as the T8 dermatome was shown to be evoked by rectal distension using a barostat.[23] Rectal distension being referred to such a high dermatome level may be attributed to the complexity of the route that nerve fibers travel to reach the splanchnic nerves. Schematically, sensory signals resulting from colonic distension enter the nerve plexuses, which can ultimately reach the celiac ganglion and the greater splanchnic nerve. This means the colonic sensory signals can reach up to as high as the T4 to T5 dermatomes, which might be a possible anatomical explanation for the cause of NCCP in some patients with constipated FBDs being the result from aberrant viscerosomatic sensory projections.

ARM findings of increased urgency and maximal volume for rectal sensation, indicating decreased rectal sensation, might be regarded as being opposed to the previous studies which show lowered perception thresholds to rectal distension, in other words rectal hypersensitivity is one of representative clinical features of IBS.[24,25] This distinction between rectal sensitivity profiles probably resulted from the difference of subject populations. Patients with functional constipation as well as those with IBS were included in our study. Rectal distension normally induces the desire to defecate using cooperative movements of the muscular structures in the pelvic area including the anal sphincter. This collaborative process is modulated by the neurons in the sacral plexus. Presumably, this coordination could be negatively affected, resulting in constipation if there is an aberrant projection of the afferent sensory nerve fibers.

After the laxative treatment, most patients with NCCP reported that the frequency or intensity of NCCP decreased with resolution of constipation. This finding suggests that there may be a distinctive pathophysiology that could explain the cause of atypical symptoms including NCCP. Moreover, the presence of sharp abdominal pain or back pain among the patients with NCCP might be a clinical indicator, implying that the chest pain might originate from the gut and could be improved after treatment with laxatives. These findings show that scrupulous history taking and detailed assessment of torso symptoms in PPI-refractory NCCP patients are important to identify the origin of the NCCP and to reduce the efforts and expenses spent on managing NCCP.

This study has some limitations. Since it was a retrospective observational study from a single tertiary center, the potential association between NCCP and constipation should be carefully interpreted and warrants further examination such as in a prospective cohort study and mechanistic study to assess the sensory neuronal function in the pathogenesis of NCCP in constipated FBDs. Nevertheless, we carefully chose NCCP patients with strict exclusion criteria. Every NCCP patient underwent EGD to exclude structural diseases of upper GI origin. And as the threshold of primary care is low due to national health insurance system in Korea, usually PPI trial had repeatedly been conducted before the patients were referred to tertiary care hospitals. Under this circumstance, we believe that the possibility of GERD and upper GI structural diseases have been properly ruled out in the inclusion process. The rather small number of patients in the NCCP group could have affected the intergroup differences in the ARM findings. Despite such limitations, we found clinical evidences to support that NCCP accompanied by constipation might have a distinctive underlying pathophysiology compared to NCCP in esophageal diseases such as GERD. It is well known that various upper GI symptoms and dyssynergic defecation are common in patients with IBS.[26,27] However, to our knowledge, this is the first report which shows symptomatic improvement of NCCP achieved by laxatives in patients with functional constipation or IBS-C which was accompanied with dyssynergic defecation.

In conclusion, the findings of the current study suggest that NCCP in patients with constipated FBDs was associated with other atypical GI symptoms such as sharp abdominal pain and back pain, and was resolved after treatment of combination laxatives. Decreased rectal sensation, together with the aforementioned findings, suggests that there might a distinctive pathophysiology of NCCP involving aberrant viscerosomatic sensory projections from the gut. A hypothesis that there is a different clinical phenotype of constipated functional bowel disorders with viscerosomatic referral symptoms including PPI-refractory NCCP has a value to be clarified and warrants further prospective studies.

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