



Comparison of Clinical Characteristics and Long-term Prognosis of Focal Hypoganglionosis With Adult-onset Megacolon and Chronic Intestinal Pseudo-obstruction

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Background/Aims

Focal hypoganglionosis with adult-onset megacolon (FHAM) is marked by colon dilation proximal to a narrowed segment, with unaffected small bowel motility. Despite similar initial symptoms, FHAM may be more amenable to surgical intervention without recurrence, unlike chronic intestinal pseudo-obstruction (CIPO). The long-term outcomes of FHAM remain underexplored, prompting a comparison of its clinical features and prognosis with CIPO.

Methods

We conducted a retrospective analysis of patients presenting with chronic constipation and megacolon, prospectively recruited between January 2017 and December 2023. Within this cohort, 87 patients were diagnosed with FHAM and 13 with CIPO, all of whom were included in the study. The median follow-up period was 3.0 years for patients with FHAM and 2.8 years for those with CIPO.

Results

The proportion of females was greater in both groups (FHAM, 67.8%; CIPO, 53.8%). The median age at diagnosis was similar between the groups (FHAM, 54.5 years; CIPO, 45.3 years). Surgery was performed in 46.0% of patients with FHAM and 69.2% of those with CIPO. Unplanned postoperative hospitalizations and the need for reoperation due to disease recurrence were notably lower in patients with FHAM. None of the patients with FHAM required long-term total parenteral nutrition, in contrast to 46.2% of patients with CIPO. Significant inter-group differences were observed in body mass index at the last follow-up.

Conclusions

Patients with FHAM exhibit a more favorable long-term prognosis and lower postoperative recurrence rates than patients with CIPO. This study underscores the importance of differentiating between these conditions and precisely selecting surgical candidates.

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Key Words

Gastrointestinal motility; Hypoganglionosis; Intestinal pseudo-obstruction; Megacolon; Prognosis

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Introduction

Chronic intestinal pseudo-obstruction (CIPO) is a clinical syndrome characterized by severe digestive symptoms and signs of intestinal obstruction, with typical bowel loop distension and air-fluid levels on plain radiographs, but without any radiological or endoscopic evidence of a mechanical lesion occluding the gut lumen.¹⁻⁴ The rarity of the disease, coupled with the absence of recognized laboratory findings or established diagnostic methods, contributes to a lack of awareness and often leads to prolonged undiagnosed status and unnecessary surgeries.^{3,5} A comprehensive diagnostic work-up is essential in patients with CIPO to prevent unnecessary surgeries, and considering that CIPO can be classified as either idiopathic or a secondary disorder affecting the enteric neuromusculature, such as progressive systemic sclerosis, paraneoplastic syndromes, and amyloidosis.^{1,6-9} CIPO mainly affects the small bowel but may involve any segment of the gastrointestinal (GI) tract. It can be understood as an insufficiency of smooth muscle contractility that alters gut transit and motility.^{1,5,8,10} Therefore, patients experience acute, chronic, or recurrent episodic symptoms of abdominal pain, vomiting, and distension, often leading to poor long-term outcomes, including frequent hospitalizations, harmful abdominal surgeries, weight loss, and the inability to maintain normal oral feeding, thereby requiring long-term total parenteral nutrition (TPN).^{1-4,11-14}

Recently, studies conducted in Korea have examined a distinct subset of patients who exhibit characteristics different from those of typical megacolon and CIPO; this condition is termed focal hypoganglionosis with adult-onset megacolon (FHAM).¹⁵⁻²⁰ While small bowel motility remains normal in these patients, FHAM is characterized by dilatation of the colon proximal to a short area of reduced luminal diameter.²⁰ The stenotic region, referred to as focal functional narrowing (FFN), is observed by computed tomography (CT) or colonoscopy; pathologically, a reduced number of myenteric ganglion cells has been identified in this narrowed

region located between segments with abundant ganglion cells.^{19,20} Hypoganglionosis is associated with inflammatory cells (CD3+ T cells) along the myenteric plexus.²⁰ In contrast, there is no definitive consensus regarding the presence of ganglion cells in typical megacolon, which is characterized by abnormal, diffuse dilation of the colon.²⁰ As FHAM is a rare disease primarily reported in Korean populations,¹⁵⁻²⁰ clinicians may face challenges in accurate diagnosis due to a lack of awareness of FHAM and the similarity of its symptoms with CIPO. Despite these diseases sharing similar initial symptoms, surgery may be a helpful treatment option for patients with FHAM experiencing severe symptoms, in contrast to the treatment approach for patients with CIPO.^{2,3,19,20} Studies directly comparing the prognoses of FHAM and CIPO are limited in number. A previous study prospectively evaluated the follow-up of patients with FHAM for up to 18 months postsurgery.²⁰ We compared the clinical features and prognosis of FHAM to those of CIPO and evaluated the long-term prognosis of FHAM.

Materials and Methods

Patients

We prospectively recruited patients presenting with chronic constipation and megacolon since January 2017 at Asan Medical Center, a tertiary university hospital in South Korea, as previously described.²⁰ Within this cohort, 87 patients diagnosed with FHAM and 13 patients diagnosed with CIPO between January 2017 and December 2023 were included in the study.

The diagnosis of FHAM was established for individuals who fulfilled the following criteria²⁰: (1) chronic constipation associated with recurrent episodes of symptoms mimicking sub-acute mechanical obstruction, including abdominal pain and distension; (2) marked colonic dilatation of > 5 cm proximal to the FFN, and/or intestinal air-fluid levels on abdominal plain radiograph, and/or axial CT; and (3) an area of focal narrowing observed on CT and/

or colonoscopy in the absence of mechanical obstruction.

The diagnosis of CIPO was based on clinical symptoms, including recurrent episodes of GI symptoms mimicking mechanical obstruction, with a minimum symptom duration of 6 months. Additionally, it involved the presence of dilated small bowel loops without a demonstrated obstructive lesion on radiological examinations, and confirmed delayed GI motility through motility examinations such as cine-magnetic resonance imaging (MRI), gastric emptying scan, or esophageal manometry.^{14,21,22} We were unable to conduct intestinal manometry and full-thickness biopsy. While these tests can play a supportive role in diagnosing CIPO, they are not required components of the diagnosis.^{4,5} Primary and secondary CIPO were included. The Institutional Review Board of Asan Medical Center approved the protocol of this study (No. 2017-0021).

Data Collection and Disease Outcome Measurement

Patient data were retrieved from medical records; this data included demographics, age at symptom onset, age at diagnosis, body mass index at the first visit, past medical and surgical history, presenting symptoms, follow-up duration, and use of medications such as bulk laxatives (eg, psyllium and polycarbophil), osmotic laxatives (eg, magnesium hydroxide, lactulose, and polyethylene glycol), stimulant laxatives (eg, senna and bisacodyl), and prokinetics.

The results of diagnostic examinations, including abdominal CT, cine-MRI, endoscopy, and several gastrointestinal motility examinations, were also reviewed. Abdominal CT and endoscopy were used to confirm focal stenosis and proximal bowel dilatation without mechanical obstruction. Cine-MRI was conducted to evaluate small bowel motility according to the protocol of Asan Medical Center. The degree of small bowel motility was determined as follows: grade 1, adynamic (non-peristaltic) wave; grade 2, decreased but preserved peristalsis; and grade 3, normal peristalsis. Gastrointestinal motility tests included high-resolution anorectal manometry, balloon expulsion test, colon transit test study (CTTS), high-resolution esophageal manometry (HRAM), and gastric emptying scan. The protocol of tests was described in a previously published study.^{23,24}

The clinical outcomes, including the disease-related emergency department visits or hospitalizations, the necessity for reoperation, and the nutritional status (eg, oral diet and parenteral nutrition), were examined. Emergency department visits or hospitalizations unrelated to FHAM or CIPO were excluded. Data on operative findings (emergency operations, surgical approach, and postoperative complications) were also collected for patients with FHAM who underwent surgery. For patients who had not visited the out-

patient department for an extended duration, clinical data were collected through telephone interviews.

Statistical Methods

Continuous variables were presented as medians with interquartile ranges (IQR), and categorical variables were presented as numbers with percentages. The chi-squared or Fisher's exact test was used to compare categorical variables. Student's *t* test or the Mann-Whitney *U*-test was used to compare continuous variables. The optimal cutoff point for CTTS in predicting surgical intervention was determined using the Youden index, which maximizes the combined sensitivity and specificity. Incidence rates of events were expressed as the number of events per patient-year and compared using Poisson regression. All *P*-values < 0.05 were considered statistically significant. Statistical analyses were performed using R statistics software version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Both groups had a predominance of female patients (FHAM: 67.8%; CIPO: 53.8%). The median age at diagnosis was comparable between the groups (FHAM: 54.5 years [IQR, 43.1-63.0 years]; CIPO: 45.3 years [IQR, 23.9-63.7 years]; *P* = 0.458). A notable delay in reaching a diagnosis was observed in patients with CIPO (FHAM: 0.8 years [IQR, 0.2-2.0 years]; CIPO: 2.5 years [IQR, 0.6-6.0 years]; *P* = 0.045). The median follow-up duration was 3.0 years (IQR, 1.0-6.1 years) and 2.8 years (IQR, 1.0-9.8 years) for the FHAM and CIPO groups, respectively. The body mass index at the last follow-up differed significantly between the 2 groups (FHAM: 21.3 kg/m² [IQR, 19.2-22.9 kg/m²]; CIPO: 17.3 kg/m² [IQR, 16.1-18.9 kg/m²]; *P* < 0.001), indicating poor nutrition in the CIPO group. At their initial hospital visit, both groups presented with sub-occlusive symptoms. The majority of patients with FHAM (98.9%) complained of constipation, while the CIPO group reported abdominal distension most frequently (92.3%). A high incidence of diabetes mellitus was noted in patients with FHAM (FHAM: 37.9%; CIPO: 0.0%; *P* = 0.017). Among the patients with CIPO, 5 (38.5%) were classified as having secondary CIPO due to underlying diseases, including systemic sclerosis and cancer. Twenty-eight patients (32.2%) with FHAM and 2 (15.4%) with CIPO had a history of abdominal surgery, including appendectomy, uterine myomectomy, hysterectomy,

Table 1. Baseline Characteristics of Patients With Focal Hypoganglionosis With Adult-onset Megacolon and Chronic Intestinal Pseudo-obstruction

Variable	FHAM (n = 87)	CIPO (n = 13)	P-value
Sex			0.498
Male	28 (32.2)	6 (46.2)	
Female	59 (67.8)	7 (53.8)	
BMI at first visit (kg/m ²)	21.4 (18.8-22.5)	19.2 (16.9-19.6)	0.005
BMI at last follow-up (kg/m ²)	21.3 (19.2-22.9)	17.3 (16.1-18.9)	< 0.001
Age at symptom onset (yr)	56.5 (43.9-64.2)	45.3 (23.9-63.7)	0.291
Age at diagnosis (yr)	54.5 (43.1-63.0)	45.3 (23.9-63.7)	0.458
Duration from onset to diagnosis (yr)	0.8 (0.2-2.0)	2.5 (0.6-6.0)	0.045
Follow-up duration (yr)	3.0 (1.0-6.1)	2.8 (1.0-9.8)	0.569
Symptoms at diagnosis			
Abdominal pain	59 (67.8)	9 (69.2)	> 0.999
Constipation	86 (98.9)	10 (76.9)	0.003
Diarrhea	0 (0.0)	2 (15.4)	0.008
Abdominal distension	63 (72.4)	12 (92.3)	0.229
Nausea/vomiting	14 (16.1)	4 (30.8)	0.369
Weight loss	33 (37.9)	5 (38.5)	> 0.999
Past medical history			
Hypertension	21 (24.1)	3 (23.1)	> 0.999
Diabetes mellitus	33 (37.9)	0 (0.0)	0.017
Chronic kidney disease	1 (1.1)	0 (0.0)	> 0.999
Ischemic heart disease	2 (2.3)	0 (0.0)	> 0.999
Peripheral/cerebral vascular disease	2 (2.3)	2 (15.4)	0.137
Hyperthyroidism	1 (1.1)	0 (0.0)	> 0.999
Hypothyroidism	0 (0.0)	1 (7.7)	0.269
Other autoimmune disease	0 (0.0)	0 (0.0)	1.000
Connective disease ^a	0 (0.0)	3 (23.1)	0.004
Psychological disease	2 (2.3)	1 (7.7)	0.848
Paraneoplastic syndrome ^b	0 (0.0)	2 (15.4)	0.008
Previous abdominal surgery ^c	28 (32.2)	2 (15.4)	0.364

^aConnective disease included systemic sclerosis.

^bParaneoplastic syndrome included small cell lung cancer and monoclonal gammopathy of undetermined significance.

^cAbdominal surgery included appendectomy, uterine myomectomy, hysterectomy, oophorectomy, nephrectomy, herniorrhaphy, cholecystectomy, and colectomy.

FHAM, focal hypoganglionosis with adult-onset megacolon; CIPO, chronic intestinal pseudo-obstruction; BMI, body mass index.

Data are expressed as n (%) or median (interquartile range).

oophorectomy, nephrectomy, herniorrhaphy, cholecystectomy, and colectomy. The baseline characteristics are shown in Table 1.

Diagnostic Test Results

Table 2 presents the results of diagnostic tests, including radiology and motility tests. FFN was observed only in patients with FHAM, with the most frequently involved site being the descending colon (37.9%), followed by the splenic flexure (23.0%). Post-operative histological examination revealed FFN with a median length of 20.0 cm (IQR, 10.5-28.4 cm). Among 87 patients with FHAM, 26 (29.9%) exhibited small bowel dilation on abdominal

CT, while 51 out of 53 (96.2%) showed preserved normal peristalsis on cine-MRI. However, all 3 patients with CIPO who underwent cine-MRI examinations had impaired small bowel motility. HRAM showed an abnormal pattern in 58 patients from both groups. The median colon transit time was 68.4 hours (IQR, 58.8-72.0 hours) in the FHAM group and 63.0 hours (IQR, 56.4-69.0 hours) in the CIPO group. A gastric emptying scan was performed in 23 patients with FHAM and 4 patients with CIPO. All patients with FHAM had normal gastric emptying times, while all patients with CIPO had delayed times.

Table 2. Diagnostic Test Results of Patients With Focal Hypoganglionosis With Adult-onset Megacolon and Chronic Intestinal Pseudo-obstruction

Variable	FHAM (n = 87)	CIPO (n = 13)	P-value
FFN at colon			< 0.001
No	0 (0.0)	13 (100.0)	
Yes	87 (100.0)	0 (0.0)	
FFN location		NA	
Sigmoid colon	16 (18.4)		
Descending colon	33 (37.9)		
Splenic flexure	20 (23.0)		
Transverse colon	18 (20.7)		
FFN length ^a (cm)	20.0 (10.5-28.4)	NA	
Small bowel dilatation on CT			< 0.001
No dilatation	61 (70.1)	0 (0.0)	
Dilatation	26 (29.9)	13 (100.0)	
Cine MRI			< 0.001
Grade 3, Normal peristalsis	51/53 (96.2)	0 (0.0)	
Grade 2, Decreased but preserved peristalsis	2/53 (3.8)	1/3 (33.3)	
Grade 1, Non-peristalsis	0 (0.0)	2/3 (66.7)	
Colonoscopy-confirmed ^b	59 (67.8)	6 (46.2)	0.224
HRAM			0.859
Normal	28/80 (35.0)	2/8 (25.0)	
Abnormal pattern of recto-anal coordination	52/80 (65.0)	6/8 (75.0)	
CTTS (hr)	68.4 (58.8-72.0)	63.0 (56.4-69.0)	0.459
Gastric emptying scan			< 0.001
Normal	23/23 (100.0)	0 (0.0)	
Delayed	0 (0.0)	4/4 (100.0)	

^aFocal functional narrowing (FFN) length was measured only in patients who underwent surgical resection and pathological evaluation.

^bIn focal hypoganglionosis with adult-onset megacolon (FHAM), 'colonoscopy-confirmed' refers to the presence of abrupt proximal colonic dilatation with distal collapse, consistent with FFN. In chronic intestinal pseudo-obstruction (CIPO), colonoscopy was performed to exclude mechanical obstruction or focal narrowing.

HRAM, high-resolution anorectal manometry; CTTS, colon transit time study; NA, not available.

Data are expressed as n (%) or median (interquartile range).

Clinical Outcomes

Forty patients (46.0%) with FHAM and 9 patients (69.2%) with CIPO underwent surgery, with a duration from symptom onset to surgery of 1.2 years (IQR, 0.6-2.9 years) and 8.2 years (IQR, 1.1-9.0 years), respectively. In cases where the condition advanced to a septic state with medically refractory symptoms, 7 out of 40 (17.5%) patients with FHAM and 2 out of 9 (22.2%) patients with CIPO underwent emergency surgery. In patients with FHAM, surgical modalities included total colectomy, subtotal colectomy, and anterior resection, while patients with CIPO underwent surgical procedures such as lysis of adhesions, small bowel segmental resection, subtotal colectomy, total colectomy, and loop ileostomy. Before receiving a proper diagnosis and treatment, both FHAM and CIPO patients experienced frequent emergency department visits or hospitalizations, with no statistically

significant differences observed: 1.9 vs 1.0 episodes per patient-year in the medical treatment groups of patients with FHAM and CIPO, respectively ($P = 0.192$); and 1.4 vs 1.6 episodes per patient-year in the surgical treatment groups of patients with FHAM and CIPO, respectively ($P = 0.539$). Following medical treatment, 44.7% of patients with FHAM and 50.0% of patients with CIPO experienced at least 1 episode of disease-related emergency department visit or hospitalization during the follow-up period ($P > 0.999$). Notably, the rate of these episodes was significantly higher in the CIPO group than in the FHAM group (1.4 vs 0.3 episodes per patient-year, $P < 0.001$). Among those who underwent surgical intervention, a markedly greater proportion of patients with CIPO had at least 1 disease-related episode during follow-up (CIPO: 100.0%; FHAM: 15.0%; $P < 0.001$), along with a substantially higher rate of emergency department visits or hospitalizations (CIPO: 3.1 episodes per patient-year; FHAM:

0.2 episodes per patient-year; $P < 0.001$). Of the 40 patients with FHAM who underwent surgery, 6 were readmitted, and 1 patient (2.5%) required reoperation. In contrast, among the patients with CIPO who underwent surgery, 6 patients (66.7%) required reoperation ($P < 0.001$). No patient with FHAM required TPN for more than a month, and 6 out of 13 (46.2%) patients with CIPO required TPN at the last follow-up ($P < 0.001$). The CIPO group exhibited a poorer prognosis, with 2 patients experiencing mortality, both of whom had paraneoplastic syndrome (Table 3).

Comparison of Surgical and Medical Treatment Groups in Focal Hypoganglionosis With Adult-onset Megacolon

The only statistically significant difference in baseline characteristics was a longer CTTS result in the surgical group than in the medical treatment group (69.6 hours [IQR, 67.2-72.0 hours] vs 64.8 hours [IQR, 50.4-70.8 hours], $P = 0.027$) (Table 4). Cut-point analysis identified a CTTS > 62.4 hours as being associated with an increased likelihood of surgical intervention (sensitivity = 87.9%, specificity = 46.3%); 87.9% of patients above this threshold underwent surgery, compared to only 9.8% of those below it.

Clinical outcomes were also compared between treatment modalities. The surgical group demonstrated more favorable outcomes, with significantly fewer patients requiring constipation-related medications at the last follow-up (25.0% vs 93.6%, $P < 0.001$) and fewer unplanned emergency department visits or hospitalizations

during follow-up (15.0% vs 44.7%, $P = 0.006$). Regarding surgical procedures, 31 patients (77.5%) underwent subtotal colectomy, 6 (15.0%) underwent total colectomy, 2 (5.0%) had a low anterior resection, and 1 patient (2.5%) received a transverse loop colostomy following previous rectal cancer surgery (Table 5).

Figure shows a comparison of the number of medications between the medically and surgically managed groups among the patients with FHAM. At the 4-year follow-up, patients in the medically managed group used a median of 2.5 medications (IQR, 2-3; range, 0-6) to alleviate symptoms, whereas almost all patients in the surgically managed group had discontinued their medications, with only 3 patients continuing a median of 0.5 medications (IQR, 0-2; range, 0-4; $P = 0.045$).

Discussion

In this study, long-term outcomes in patients with FHAM, specifically in those with dilatation of the colon proximal to the FFN, were more favorable than in patients with CIPO. Patients with CIPO required frequent emergency department visits, reoperations, and prolonged TPN, indicating a need for palliative care. On the other hand, most of the patients with FHAM were treated with a single surgery without the need for additional drug treatment. Even the patients who required emergency department visits or admission after medical or surgical treatment did not require prolonged TPN and could continue their daily lives with some

Table 3. Outcomes of Patients With Focal Hypoganglionosis With Adult-onset Megacolon and Chronic Intestinal Pseudo-obstruction

Variable	FHAM (n = 87)	CIPO (n = 13)	P-value
Surgery	40 (46.0)	9 (69.2)	0.205
Reason for surgery			> 0.999
Emergency	7/40 (17.5)	2/9 (22.2)	
Elective	33/40 (82.5)	7/9 (77.8)	
Duration from symptom to surgery (yr)	1.2 (0.6-2.9)	8.2 (1.1-9.0)	0.067
Unplanned ED visits or hospitalizations			
Rate of all contacts per patient-year, before medical treatment (95% CI)	1.9 (1.6-2.3)	1.0 (0.3-2.0)	0.192
Number of patients who had any contacts after medical treatment	21/47 (44.7)	2/4 (50.0)	> 0.999
Rate of all contacts per patient-year, after medical treatment (95% CI)	0.3 (0.2-0.4)	1.4 (0.4-2.6)	< 0.001
Rate of all contacts per patient-year, before surgical treatment (95% CI)	1.4 (1.2-1.7)	1.6 (1.1-2.2)	0.539
Number of patients who had any contacts after surgical treatment	6/40 (15.0)	9/9 (100.0)	< 0.001
Rate of all contacts per patient-year, after surgical treatment (95% CI)	0.2 (0.1-0.3)	3.1 (2.5-3.8)	< 0.001
Re-operation due to disease recurrence	1/40 (2.5)	6/9 (66.7)	< 0.001
TPN at last follow-up	0 (0.0)	6/13 (46.2)	< 0.001
Death	0 (0.0)	2/13 (15.4)	0.008

FHAM, focal hypoganglionosis with adult-onset megacolon; CIPO, chronic intestinal pseudo-obstruction; ED, emergency department; TPN, total parenteral nutrition.

Data are expressed as n (%) or median (interquartile range).

Table 4. Comparison of Clinical Characteristics Between Medical and Surgical Groups in Patients With Focal Hypoganglionosis With Adult-onset Megacolon

Variable	Medical (n = 47)	Surgery (n = 40)	P-value
Sex			> 0.999
Male	15 (31.9)	13 (32.5)	
Female	32 (68.1)	27 (67.5)	
BMI at first visit (kg/m ²)	21.7 (18.9-22.8)	20.7 (18.4-22.3)	0.224
Age at diagnosis (yr)	55.8 (37.8-65.0)	57.1 (46.4-62.2)	0.756
Duration from onset to diagnosis (yr)	0.8 (0.2-2.0)	0.6 (0.2-2.0)	0.648
Follow-up duration (yr)	2.9 (0.8-6.5)	2.9 (1.0-5.0)	0.740
Symptoms at diagnosis			
Abdominal pain	29 (61.7)	30 (75.0)	0.274
Constipation	46 (97.9)	40 (100.0)	> 0.999
Diarrhea	0 (0.0)	0 (0.0)	1.000
Abdominal distension	32 (68.1)	31 (77.5)	0.460
Nausea/vomiting	7 (14.9)	7 (17.5)	0.970
Weight loss	17 (36.2)	16 (40.0)	0.885
Maximum diameter of colon (mm)	71.0 (62.5-81.0)	76.0 (61.5-95.0)	0.181
CTTS (hr)	64.8 (50.4-70.8)	69.6 (67.2-72.0)	0.027
FFN location			0.256
Sigmoid colon	10 (21.3)	6 (15.0)	
Descending colon	14 (29.8)	19 (47.5)	
Splenic flexure	14 (29.8)	6 (15.0)	
Transverse colon	9 (19.1)	9 (22.5)	
Small bowel dilatation on CT			0.494
No dilatation	31 (66.0)	30 (75.0)	
Dilatation	16 (34.0)	10 (25.0)	

BMI, body mass index; CTTS, colon transit time study; FFN, focal functional narrowing.

Data are expressed as n (%) or median (interquartile range).

Table 5. Comparison of Outcomes Between the Medical and Surgical Groups in Patients With Focal Hypoganglionosis With Adult-onset Megacolon

Variable	Medical (n = 47)	Surgery (n = 40)	P-value
Clinical outcomes at follow-up			
Constipation medication use at last follow-up	44 (93.6)	10 (25.0)	< 0.001
Number of patients who had any unplanned ED visits or hospitalizations after each treatment	21 (44.7)	6 (15.0)	0.006
Surgical details			
Surgical approach			
Open	NA	6 (15.0)	
Laparoscopy		34 (85.0)	
Operation name			
Subtotal colectomy	NA	31 (77.5)	
Total colectomy		6 (15.0)	
Low anterior resection		2 (5.0)	
Transverse loop colostomy ^a		1 (2.5)	
Postoperative complications ^b	NA	3 (7.7)	

^aThis patient had low anterior resection for rectal cancer in 2012, so a transverse loop colostomy was performed.

^bThese 3 cases included colostomy malfunction, complicated fluid collection at the anastomosis site, and postoperative peritonitis.

ED, emergency department; NA, not available.

Data are expressed as n (%).

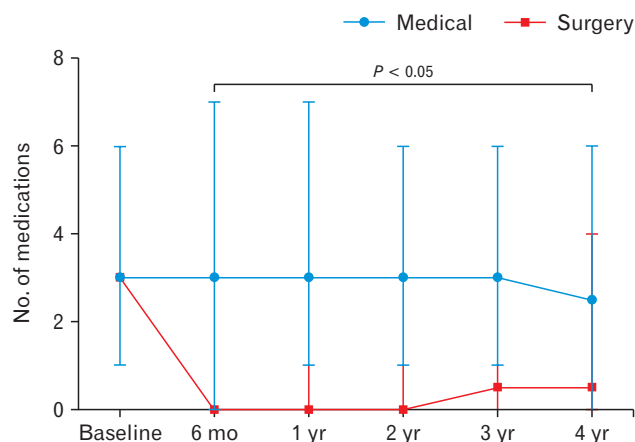


Figure. Comparison of the number of medications between the medically and surgically managed groups of patients with focal hypoganglionosis with adult-onset megacolon (FHAM). In the medical group, patients continued to use a median of 3 medications to alleviate their symptoms, whereas almost all patients in the surgical group discontinued their medication.

medication support.

Previous studies have reported that CIPO is associated with poor prognosis, unsatisfactory response to medical and surgical management leading to malnutrition, necessity of long-term TPN support and opioid treatment for intractable abdominal pain, and the development of psychiatric problems such as depression or suicide attempts.^{3,5,12,14} Half of the patients with CIPO in our cohort were also unable to sustain oral feeding and ultimately required TPN. Given the progressive nature of CIPO, unnecessary surgical bypass or bowel resection is deemed ineffective and may only provide temporary relief, potentially leading to an exacerbation of symptoms. Therefore, a cautious approach is needed while deciding on the surgical procedures.^{3,5,25} Sabbagh et al²⁶ reported surgical complications in 58.2% of cases, leading to reoperation in 17.0% of the patients, with an additional 66.0% requiring CIPO-related reoperations within 5 years of the initial surgery. This suggests that surgery should be considered only for a highly selected and well-characterized subset of patients as CIPO may progressively affect any segment of the GI tract.^{3,14,25,27} As described above and in other studies, while the therapeutic benefits of surgery are highly controversial,^{3,5,26,27} surgery is frequently performed. Patients with CIPO who visit our hospital have already undergone several unnecessary surgeries due to severe symptoms and misdiagnosis at referral hospitals, likely due to the low recognition rate of this disease.⁵ In our study, 9 patients (69.2%) with CIPO underwent surgery, and 6 patients (66.7%) required reoperation. All 6 of the 13 patients

(46.2%) who required prolonged TPN were in the surgery group. Therefore, it is crucial to distinguish CIPO from FHAM, as they may initially present similarly but require different approaches, with surgery potentially being beneficial in FHAM.

Based on clinical and radiologic findings, we proposed 3 criteria for the diagnosis of FHAM.²⁰ Among the patients who met these criteria, only 46.0% received pathological confirmation through surgical resection. Since histopathologic confirmation of colonic hypoganglionosis requires bowel resection, and not all patients with FHAM undergo surgery, it could not be included as a mandatory component of the diagnostic criteria. To improve the reliability of clinical diagnosis in non-surgical cases, additional evidence supporting the absence of delayed small bowel motility may be valuable. We hypothesize that preserved small bowel motility may be a key factor contributing to the more favorable surgical outcomes observed in patients with FHAM than in those with CIPO. Supporting this hypothesis, cine-MRI and gastric emptying scan results demonstrated statistically significant differences between the 2 groups: normal small bowel peristalsis was observed in 96.2% of patients with FHAM versus 0.0% in patients with CIPO ($P < 0.001$), and normal gastric emptying times were noted in 100.0% of patients with FHAM compared to 0.0% of patients with CIPO ($P < 0.001$). However, the number of patients who underwent these motility assessments was limited (53 of 87 for cine-MRI and 23 of 87 for gastric emptying scans in the FHAM group; 3 of 13 for cine-MRI and 4 of 13 for gastric emptying scans in the CIPO group), which may limit the interpretability and generalizability of these findings. Future studies with larger and more balanced cohorts are warranted to further explore this relationship and determine whether the absence of delayed small bowel motility could be incorporated into standardized diagnostic criteria for FHAM as a complementary tool to pathological confirmation.

The most recently reported study termed the disease status of colon dilatation proximal to focal stenosis as “adult-onset megacolon with focal hypoganglionosis.”²⁰ For readability and abbreviation, we have rearranged the words as ‘focal hypoganglionosis with adult-onset megacolon (FHAM).’ Patients with FHAM showed favorable outcomes, with satisfaction and no symptom recurrence following total or subtotal colectomy.^{19,28} Yoon et al²⁰ have reported that 10 out of 29 patients with FHAM who underwent colectomy showed greater improvements in global bowel satisfaction and bowel movement frequency compared to those who received only medical treatment for up to 18 months ($P < 0.001$). In our study, we prospectively included the highest number of patients with FHAM in a single study so far. We have reported the extended outcomes fol-

lowing both medical and surgical treatments, with a median duration of 3 years (IQR, 1.0–6.1 years). Surgery resulted in satisfactory outcomes, including the discontinuation of medication; only 6 out of 40 (15.0%) patients required postoperative hospitalization, with 1 patient undergoing reoperation. None of the patients required prolonged TPN. The disparity in postsurgical prognosis underscores the importance of distinguishing between CIPO and FHAM and carefully selecting appropriate candidates for surgical intervention.

When patients with suspected FHAM first visit our center, we initially consult the surgery department to seek a second opinion on whether surgery is necessary. In many cases, particularly during the early stages, patients often prefer medical treatment, even when surgery is expected to be beneficial. The findings in our study, indicating a median duration of 1.2 years (IQR, 0.6–2.9 years) between symptom onset and operation, support this observation. However, if the megacolon worsens despite medical therapy and they have to make multiple visits to the emergency room, require decompression, or if the condition advances to a septic state, surgery becomes an inevitable course. Yoon et al²⁰ suggested that the surgical group had a larger megacolon diameter than the medical group (90.0 mm [IQR, 79.2–104.0 mm] vs. 69.0 mm [IQR, 61.5–81.5 mm], $P = 0.002$), indicating a greater symptom burden. However, in our study, no statistically significant difference was observed between the 2 groups (surgical group: 76.0 mm [IQR, 61.5–95.0 mm]; medical group: 71.0 mm [IQR, 62.5–81.0 mm]; $P = 0.181$). Instead, patients in the surgical group exhibited significantly longer CTTS results. Although the mechanisms underlying the association between prolonged CTTS and the need for surgical intervention remain unclear, it is plausible that delayed colonic transit reflects more severe symptoms and impaired colonic motility, thereby increasing the likelihood of requiring surgical management.

In our study group, 1 out of 40 patients with FHAM who underwent surgery required reoperation. Following the initial surgery, in which an FFN was found in the mid-transverse colon, a subtotal colectomy involving the terminal ileum to the distal descending colon was performed. For the first 18 months postsurgery, the patient did not use constipation-related medication. However, in the second year, the patient experienced abdominal pain, vomiting, and constipation, accompanied by overall distension in both the small and large intestines, as observed on abdominal CT. Despite supportive care and monitoring, the patient strongly expressed a desire for reoperation. Additionally, considering the relatively low number of ganglion cells (8.1 ganglia/cm) present in the distal nondilated margin observed in the previous surgical specimen, we proceeded with total colectomy. Until 4 months after the reoperation, no ad-

ditional medications were administered, and no signs of symptom recurrence were noted. Recurrence is presumed to have occurred due to inadequate colon resection, including the FFN, with an attempt to preserve as much of the colon as possible. Collection and analysis of similar cases in the future, specifically focusing on histological aspects, will be necessary to achieve a more comprehensive understanding of postoperative recurrence in FHAM.

While previous studies have focused more on surgical treatment in patients with FHAM,^{19,20} our study directly compared the diagnostic results and prognoses of individuals treated with medication and of those treated with surgery, considering the observation that ultimately more patients received medication (47/87, 54.0%) than those who underwent surgery. In the medical treatment group of FHAM, patients needed to maintain medications such as bulk and osmotic laxatives and prokinetics for constipation, and a higher proportion of these patients required unplanned emergency department visits or hospitalization compared to the surgical group (medical group: 44.7%; surgical group: 15.0%; $P = 0.006$). However, following medical treatment, the rate of unplanned emergency department visits or hospitalizations was significantly lower than that in the pre-treatment period (1.9 vs 0.3 episodes per patient-year in the pre-treatment and post-treatment periods, respectively; $P < 0.001$).

The main limitation of this study is the absence of manometric and histopathological findings in patients with CIPO, along with the retrospective recruitment of patients with CIPO, which resulted in the lack of comprehensive motility tests. However, nowadays, cine-MRI is suggested to better characterize CIPO,²² and our study conducted an extensive number of cine-MRIs to differentiate FHAM from CIPO by confirming whether small bowel peristalsis is preserved or not. Second, it is a single-center study, which exclusively involves Korean adult patients. Third, the surgical indications for patients with FHAM are not well-established and are subjectively perceived. Finally, the substantial disparity in sample size between the FHAM and CIPO groups represents a limitation of the study. Although appropriate statistical methods for small-sample analysis were applied, this imbalance may have reduced the statistical power and limited the ability to detect subtle differences between the 2 groups. Future prospective and multicenter studies involving patients who meet the diagnostic criteria and predefined surgical indications, with a larger number of cases, are needed.

In conclusion, compared to CIPO, FHAM had a more favorable long-term prognosis with fewer postsurgery recurrences. Hence, differentiating between these 2 diseases and carefully choosing surgical candidates is crucial. At our center, surgical interven-

tion for FHAM was typically considered in cases of medically refractory symptoms or progression to sepsis. Although prolonged CTTS was associated with surgical treatment, further studies with larger cohorts and longer follow-ups are needed to establish definitive surgical indications and identify optimal candidates.

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