Pediatric Surgery International (2019) 35:1115–1121
https://doi.org/10.1007/s00383-019-04534-w

ORIGINAL ARTICLE

Unexpected gap between intraoperative caliber change of the intestine and normoganglia in patients with intestinal aganglionosis

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Accepted: 1 August 2019 / Published online: 7 August 2019

Abstract

Purpose Intestinal aganglionosis (IA) is so rare that the entity remains unclear. The aim of the present study was to compare the outcomes of patients with IA and those with total colonic aganglionosis (TCA).

Methods The hospital records were retrospectively reviewed from 1977 to 2018. Outcomes were analyzed for the IA group and the TCA group, including clinical presentation, initial management, and operative details.

Results There were six patients were managed in IA (all male) and seven patients in TCA (4 male). The median age at the first operation was significantly younger in IA than TCA (2 days vs 24 days, $p=0.01$). The gap between the intraoperative caliber change (CC) of the intestine and the initial stoma location was not significantly different (7.5 cm vs 12 cm, $p=0.61$), but the rate of stoma dysfunction was significantly higher in IA (83% vs 0%, $p=0.005$). The gap between the CC and the ganglionated bowel was significantly longer in IA (85 cm vs 10 cm, $p=0.003$).

Conclusion Patients with IA appear to have a high risk for stoma dysfunction after the first operation because of the unexpected gap between the CC and normoganglia. The initial location of the stoma requires careful consideration.

Keywords Intestinal aganglionosis · Total colonic aganglionosis · Caliber change · Extent of aganglionosis · Initial stoma

Introduction

Intestinal aganglionosis (IA) is known as a rare and critical entity. Its characteristics and prognosis remain unclear. In some previous studies, the frequency of total colonic aganglionosis (TCA) in patients with Hirschsprung's disease (HD) was estimated to be approximately 5–8%, while that of IA was about 3–5% [1, 2].

Some IA patients eventually require intestinal transplantation [3]. However, to undergo and tolerate intestinal transplantation, they need to have physical development, including body weight and height. Moreover, excess laparotomies are not recommended in some IA patients because of their future transplantation [3]. From this perspective, their sustainable management and growth during infancy are very important for their survival.

Function of the initial enterostomy is likely to play an important role in mortality and growth in early infancy. It may also affect the frequency of laparotomy. Some previous reports showed that dysfunction of the initial stoma in IA or TCA patients could cause a dismal result [4-6]. Therefore, it is necessary to consider the initial stoma site in the treatment of IA and TCA patients.

The present study focused on the site and function of the enterostomy at the first operation in patients with IA compared to those with TCA. In addition, other factors, such as their background and operative data, were also analyzed.

Materials and methods

This study was approved by the institutional review board (IRB #2017111) and complied with the Helsinki Declaration of 1964 (revised 2013). Because of the anonymous nature of the data, informed consent was not required.

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The medical records of IA and TCA patients between November 1977 and December 2018 were retrospectively reviewed. Patients' demographics (sex, gestational week, birth weight, and prenatal diagnosis), symptoms, operative data, histopathological findings, and function of the initial stoma were analyzed. The symptoms of stoma dysfunction included episodes of inefficient stool discharge, bowel dilatation, vomiting, or enteritis.

TCA was defined as aganglionic bowel extending from the rectum to 30 cm from the terminal ileum. IA was defined as aganglionosis extending orally beyond the point 30 cm from the terminal ileum [2]. Intraoperative caliber change (CC) of the intestine was defined as the transition point between dilated proximal and distally collapsed small-bowel loops.

The diagnosis of aganglionosis was based on the histopathological findings of biopsies from several areas in the bowel, preoperative or postoperative rectal biopsies, or bowel that had been resected in later operations. Since some of the initial operations were performed emergently, intraoperative levelling biopsies could not be performed at the first operation in all cases.

Meconium passage is an important sign to understand the neonatal bowel condition. Normal meconium passage was defined as meconium having passed within 48 h after birth. Meconium passage after 48 h was defined as delayed. All IA patients had no meconium passage before the first operation; thus, their data were recorded as none.

In addition, we also reviewed the outcomes of the patients, focusing on the difference of the length between ileum end and CC. We divided the patients into two groups with the oral point of 20 cm from ileum end: the Short group, less than 20 cm, and the Long group, over 20 cm. The patients' backgrounds, operative data, histopathological findings, and function of the initial stoma were analyzed.

All data are presented as medians (range). Averages of continuous variables (such as age) were compared using Mann–Whitney *U* tests, while Fisher's exact tests were used to compare the proportions of categorical variables (such as sex) between the groups. The threshold for significance was $p < 0.05$. All statistical analyses were conducted using JMP ver. 12.

Results

Six patients (all male) had IA and seven patients (4 male, 3 female) had TCA (Table 1). There were no significant differences in their median gestational age and birth weight (38.5 weeks vs 39 weeks, $p = 0.94$; 3237 g vs 2750 g, $p = 0.1$). The first laparotomy was significantly earlier in the IA group than in the TCA group (2 days vs 24 days after birth, $p = 0.01$). The surgical procedure performed in the first operation of all patients was creation of an enterostomy. The length between intraoperative caliber change (CC) of the intestine and the ileum end was significantly longer in the IA group than in the TCA group (60 cm vs 7 cm, $p = 0.01$). There was no significant difference between the two groups in the length from the CC of the intestine to the enterostomy (7.5 cm vs 12 cm, $p = 0.61$). However, the rate of dysfunction of the initial stoma was significantly higher in the IA group than in the TCA group (83% vs 0%, $p = 0.005$). The length from the CC to the normal ganglionic site was significantly longer in the IA group than in the TCA group (85 cm vs 10 cm, $p = 0.003$). The rate of preoperative rectal biopsy and intraoperative pathological examination was significantly lower in the IA group than in the TCA group (0% vs 57%, $p = 0.07$; 17% vs 100%, $p = 0.005$).

The detailed information of the patients is shown in Tables 2 and 3. All of the patients, except for one TCA patient, were born full term. Only two IA patients were suspected to have a bowel disease before birth based on bowel dilation observed on prenatal examinations. All patients showed some symptoms associated with bowel obstruction,

Table 1 Comparison between the IA group and the TCA group

	IA ($n = 6$)	TCA ($n = 7$)	p
Sex (male)	6 (100%)	4 (57%)	0.19
Gestational week	38.5 (36–41)	39 (31–41)	0.94
Birth weight (g)	3237 (2606–3645)	2750 (1730–3200)	0.1
Prenatal diagnosis	2 (33%)	0	0.19
Age at first operation (days)	2 (1–4)	24 (2–150)	0.01
The ileum end to CC (cm)	60 (10–130)	7 (2–23)	0.01
CC to the first stoma (cm)	7.5 (2–50)	12 (5–20)	0.61
CC to the normal ganglionic site (cm)	85 (30–110)	10 (5–10)	0.003
Dysfunction of the first stoma	5 (83%)	0	0.005
Preoperative rectal biopsy	0	4 (57%)	0.07
Intraoperative pathological examination	1 (17%)	7 (100%)	0.005

IA intestinal aganglionosis, *TCA* total colonic aganglionosis, *CC* caliber change

Table 2 Patients' demographic characteristics

No.		Sex	GS week	Birth weight (g)	Prenatal diagnosis	Preoperative symptoms	Meconium passage[a]
1	Intestinal	M	40	3515	No	Abdominal distention, vomiting	None
2	Intestinal	M	41	3290	No	Vomiting (perforation)	None
3	Intestinal	M	38	3645	Bowel dilation	Abdominal distention	None
4	Intestinal	M	38	3050	Bowel dilation	Abdominal distention	None
5	Intestinal	M	36	2606	No	Abdominal distention, vomiting	None
6	Intestinal	M	39	3184	No	Vomiting	None
1	Total colon	F	41	3200	No	Abdominal distention, vomiting, colitis	Normal
2	Total colon	M	38	2795	No	Abdominal distention, vomiting	Delayed
3	Total colon	M	31	1730	No	Abdominal distention	Delayed
4	Total colon	M	39	2750	No	Abdominal distention	Normal
5	Total colon	F	37	2690	No	Abdominal distention, vomiting	Delayed
6	Total colon	M	39	3138	No	Vomiting	Delayed
7	Total colon	F	40	2735	No	Abdominal distention, vomiting, colitis	Normal

M male, *F* female

[a]Meconium passage 'Normal' was defined as within 2 days after birth, and 'Delayed' as over 3 days after birth

such as abdominal distention, vomiting, or colitis. In IA patients, meconium passage was not found, while TCA patients showed normal or delayed meconium passage.

Five IA patients did not have an intraoperative pathological examination, because their operations were performed emergently at night or on the weekend, when no pathologists work in the hospital. On the other hand, all TCA patients had intraoperative pathological examinations, since most of their operations were elective. In addition, four of the seven TCA patients were preoperatively diagnosed as having HD by rectal biopsy.

On one hand, most of the initial enterostomies in the IA group were not created at normoganglionic bowel. On the other hand, all initial stomas in the TCA group were created at a normoganglionic site.

Although the total length of intestine was recorded in all IA patients, it was not evident on retrospective review in five TCA patients.

Table 4 shows the outcomes of comparison between the Short group and Long group. In the Long group, the proportion of IA was significantly higher than in the Short group. There was no significant difference in other factors.

Discussion

IA is an uncommon and critical condition of HD. There have been various questions about IA in terms of histopathology and prognosis. Recently, the morbidity and mortality have been improved by the development of operative procedures, parenteral nutrition, and transplantation [2, 3, 7-9]. However, IA patients still have more life-threatening risks than other HD patients with a shorter length of aganglionosis, and their mortality rate is estimated to be 25% [2].

The present study focused mainly on the initial site of the enterostomy in IA patients, because we have often seen their dysfunction. In TCA patients, there were good results for the initial stoma installed about 10 cm above the intraoperative CC, while five of the six IA patients experienced the initial stoma dysfunction despite being created in similar locations. In some previous reports, the reason why the dysfunction of the initial stoma occurred was supposed to be the difficulty in pathologically assessing the extent of aganglionic length at the first operation [1, 6]. In this regard, the initial stoma in IA is more likely to be created at an aganglionic area than in TCA, and consequently, it does not work well.

In a previous study, fluid retention in the proximal gut during embryogenesis may cause a gap between the intraoperative CC and the microscopic transition zone [10]. According to that study, the discrepancy was more marked in IA than in TCA. In addition, in the present study, meconium may also result in a difference in the CC position between the two groups. As shown in Table 1, the first operation was performed significantly earlier in the IA group than in the TCA group. Since all of the IA patients did not have meconium passage after they were born, even though they received glycerin enemas, the intestine below the CC was full of meconium (Fig. 1). In contrast, since most of the TCA patients showed normal or delayed meconium passage, most of them did not require early operation within a few days after birth. In this context, although IA patients still had plenty of meconium in their intestine at the first operation, TCA patients did not. This might affect the intraoperative position of the CC. Actually, IA patient no.6 showed CC in a different position in

Table 3 Operative information

		First operation		Intraoperative findings				Intraoperative pathological examination	Preoperative rectal biopsy	Stoma site ganglia	Stoma dysfunction
		Age (days)	Status	The ileum end to CC (cm)	CC to stoma (cm)	CC to normoganglia (cm)	Total length of intestine (cm)				
1	Intestinal	2	Emergency	10	5	80	200	No	No	Aganglia	Yes
2	Intestinal	2	Emergency	20	35	35	170	No	No	Normal	No
3	Intestinal	1	Emergency	130	2	110	230	No	No	Aganglia	Yes
4	Intestinal	2	Emergency	90	10	105	230	No	No	Aganglia	Yes
5	Intestinal	2	Emergency	35	50	>90[a]	125	Yes	No	Aganglia	Yes
6	Intestinal	4	Emergency	85	5	30	160	No	No	Hypo	Yes
1	Total colon	20	Elective	3	10	10	N/A	Yes	No	Normal	No
2	Total colon	90	Elective	10	20	10	N/A	Yes	Yes	Normal	No
3	Total colon	40	Elective	15	5	5	N/A	Yes	Yes	Normal	No
4	Total colon	150	Emergency	3	12	10	N/A	Yes	No	Normal	No
5	Total colon	10	Elective	5	10	10	N/A	Yes	Yes	Normal	No
6	Total colon	2	Emergency	7	13	8	165	Yes	No	Normal	No
7	Total colon	24	Elective	23	12	7	80	Yes	Yes	Normal	No

CC caliber change, *N/A* not available

[a]In this patient, the biopsy of even the stomach did not show a normal ganglionic plexus

Table 4 Comparison between the Short group and Long group

	Short ($n=7$)	Long ($n=6$)	p
Classification (IA, *n*, %)	1 (14%)	5 (83%)	0.03
Sex (male)	5 (71%)	5 (83%)	1.0
Gestational week	39 (31–41)	38.5 (36–41)	0.94
Birth weight (g)	2795 (1730–3515)	3117 (2606–3645)	0.61
Prenatal diagnosis	0	2 (33%)	0.19
Age at first operation (days)	2 (1–24)	20 (2–150)	0.09
CC to the first stoma (cm)	10 (5–20)	11 (2–50)	0.89
CC to the normal ganglionic site (cm)	10 (5–80)	62.5 (7–110)	0.07
Dysfunction of the first stoma	1 (14%)	4 (66%)	0.1
Preoperative rectal biopsy	3 (43%)	1 (17%)	0.56
Intraoperative pathological examination	6 (85%)	2 (33%)	0.1

Short group: the length between ileum end and CC < 20 cm

Long group: the length between ileum end and CC ≥ 20 cm

IA Intestinal aganglionosis, *TCA* total colonic aganglionosis, *CC* caliber change

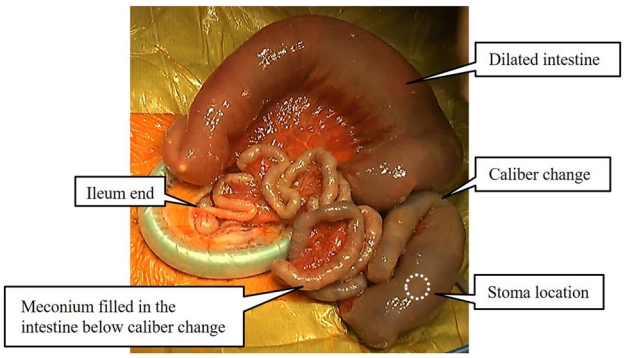

Fig. 1 Intraoperative bowel findings of IA patient no. 6 in the first laparotomy

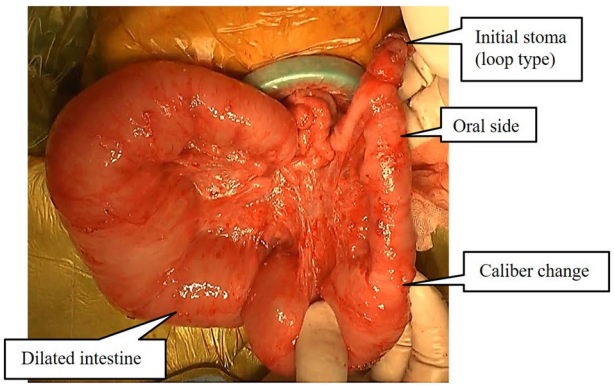

Fig. 2 Intraoperative bowel findings of IA patient no. 6 in the second laparotomy

subsequent operations (Figs. 1, 2). Finally, his ganglionated bowel was confirmed approximately 25 cm above the initial stoma through four laparotomies.

Preoperative diagnosis for long-segment HD, such as TCA or IA, is remarkably challenging [1, 6, 11]. This is mainly because the clinical and radiographic findings are quite similar to other intestinal obstructive diseases, such as intestinal atresia. The incidence rate of jejunoileal atresia is considerably higher than that of IA (about 1/5000 vs 1/150,000 in newborns) [2, 12]. In this regard, many surgeons primarily suspect intestinal atresia when they encounter neonates with bowel dilation and related symptoms, resulting in paying less attention to the possibility of aganglionosis and preparation for its management. In our experience, four of six IA cases were preoperatively misdiagnosed as intestinal atresia. One patient presented with bowel perforation before the initial surgery. Only one patient was highly suspected to have IA, mainly because of the findings of a contrast enema and contrast medium remaining for more than 24 h. That was a characteristic feature of contrast enema for long-segment HD, but its absence does not exclude the diagnosis [11, 13].

When surgeons encounter patients with an intestinal CC without structural obstruction, the diagnosis would be limited to some rare diseases, including long-segment HD, meconium plug, or cystic fibrosis [14]. In this situation, it is natural that they want to preserve a longer intestine to avoid short bowel syndrome, especially when the CC is near the ligament of Treitz. In the present cases, most of the initial stomas in IA patients were created near the CC, within 10 cm. Certainly, in short-segment HD, the transitional zone was normally limited to within 5 cm [15-17], but in patients with aganglionosis extending over the ileum end, the possibility of the transitional zone extending over 5 cm was suggested [17, 18]. In our study, although not significant, patients in the Long group tended to have a longer discrepancy between CC and normal ganglionic site than those in the Short group (Table 4). In this context, the longer the

distance between the ileum end and CC is, the more carefully the location of initial stoma might be thought.

Intraoperative levelling biopsy can be a useful method to confirm the extent of the aganglionosis and the appropriate location for the stoma [5]. However, the assessment of frozen sections at the first operation before confirming the diagnosis is not easy, especially with extensive aganglionosis over the ileum end [18]. From the histopathological perspective, the reliability of intraoperative frozen sections is not sufficient. The accuracy of frozen-section evaluation is around 90%, but in the initial operation, it can be more difficult to confirm the diagnosis [18-20]. Furthermore, it is quite difficult to differentiate long-segment HD from isolated hypoganglionosis, because they have similar features [21].

Taken together, preoperative diagnosis or management of IA is not simple. If the intraoperative CC without structural obstruction is found beyond the point 30 cm from the ileum end, the possibility of IA should be considered. In such cases, given the present results, it might be better for the initial stoma to be created by taking a greater than usual distance from the CC. Although the intraoperative frozen-section pathology is not perfectly reliable, if IA is suspected pre- or intra-operatively, the levelling biopsy should be managed. Moreover, in postoperative management, we should consider the possibility of stoma dysfunction and repetitive laparotomies and inform the patient's family. Through these attentions, better management is likely to be possible, such as using anti-adhesive materials in the first operation to anticipate future surgeries, or planning additional surgical interventions like myectomy–myotomy [9].

There are several limitations in the present study. First, it included only a small number of patients. Second, this was a single-center, retrospective, observational study. Further study is required to confirm the method of initial management for IA patients.

Conclusion

This is the first report comparing the features of IA and TCA. Patients with IA have a greater potential risk for stoma dysfunction after the first operation than TCA patients because of the unexpected gap between the CC and ganglionated bowel. The initial location of the stoma and the postoperative management for IA need to be carefully considered.

Compliance with ethical standards

Conflict of interest Akinori Sekioka, Koji Fukumoto, Hiromu Miyake, Kengo Nakaya, Akiyoshi Nomura, Yutaka Yamada, Susumu Yamada, and Naoto Urushihara have no conflicts of interest or financial ties to disclose.

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