Table 1 Summary of 27 pediatric patients performed thoracotomies with MSASCI

Case	Sex	Diagnosis	Type or site	Age at op.	Operation	Intercostal space	Complication	Prognosis
1	M	EA	Gross type A	1 year 3 month	Esophageal EEA	Rt. 4th intercostal	Minor leakage	Alive
2	F	EA	Gross type C	2 days	Esophageal EEA	Rt. 4th intercostal	Stenosis	Alive
3	M	EA, AA, TAC	Gross type C	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
4	F	EA	Gross type C	2 days	Esophageal EEA	Rt. 4th intercostal	None	Alive
5	F	EA, ELBWIPA stenosis	Gross type C	3 months	Esophageal EEA	Rt. 5th intercostal	TEF recurrence wound disruption	Died[b]
6	F	EA	Gross type D	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
7	M	EA, TA	Gross type D	1 day	Esophageal EEA	Rt. 4th intercostal	Wound disruption transient paralysis	Died[c]
8	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 5th intercostal	Stenosis	Alive
9	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 6th intercostal	Wound disruption	Alive
10	F	EA	Gross type C	1 day	Esophageal EEA	Rt. 4th intercostal	None	Alive
11	M	CCAM	Rt. middle lobe	8 months	Partial resection	Rt. 5th intercostal	None	Alive
12	M	LPS	Rt. lower lobe	4 days	LPS resection	Rt. 5th intercostal	None	Alive
13	F	CCAM	Lt. upper lobe	1 month	Partial resection	Lt. 5th intercostal	None	Alive
14	F[a]	LPS	Lt. lower lobe	8 months	LPS resection	Lt. 8th intercostal	None	Alive
15	M	CCAM	Lt. upper lobe	1 month	Lt. upper lobectomy	Lt. 5th intercostal	Pneumothorax	Alive
16	F	CCAM	Lt. lower lobe	4 months	Lt. lower lobectomy	Lt. 5th intercostal	None	Alive
17	M	LPS	Rt. lower lobe	3 months	Rt. lower lobectomy	Rt. 6th intercostal	None	Alive
18	F	CTA with LPS	Lt. lower lobe	4 months	Rt. lower lobectomy	Rt. 6th intercostal	Transient paralysis	Alive
19	M	CCAM	Lt. lower lobe	3 months	Lt. lower lobectomy	Lt. 6th intercostal	None	Alive
20	M	CCAM	Rt. lower lobe	4 months	Rt. lower lobectomy	Rt. 5th intercostal	None	Alive
21	M	LPS	Lt. lower lobe	7 months	LPS resection	Lt. 7th intercostal	None	Alive
22	F	CCAM	Rt. lower lobe	4 months	Rt. lower lobectomy	Lt. 5th intercostal	None	Alive
23	M	Mediastinal NB	Lt. upper lobe	6 years 1 month	Subtotal excision	Lt. 4th intercostal	None	Alive
24	F	Mediastinal NB	Lt. upper lobe	9 years 4 months	Subtotal excision	Lt. 3th Intercostal	None	Alive
25	M	Pulmonary HT	Lt. upper lobe	5 years 11 months	Biopsy	Lt. 6th intercostal	None	Alive
26	M	Rt. CDH		5 days	Repair	Rt. 5th intercostal	Wound disruption CDH recurrence	Alive
27	F	Rt. CDH Rt. lung agenesis		5 days	Exploratory thoracotomy	Rt. 7th intercostal	None	Alive

EA esophageal atresia, *AA* anal atresia, *TAC* truncus arteriosus communis, *ELBW* extremely low birth weight infant, *PA* pulmonary artery, *TA* tricuspid atresia, *CCAM* congenital cystic adenomatoid malformation, *LPS* lung pulmonary sequestration, *CTA* congenital tracheal atresia, *NB* neuroblastoma, *CDH* congenital diaphragmatic hernia, *HT* hypertension, *EEA* end to end anastomosis, *TEF* tracheoesophageal fistula

[a] Incision was extended caudally about 1 cm

[b, c] Two patients died due to the severe cardio-pulmonary anomalies

the wound disruption. In order to prevent this complication, a wound retractor XS has been currently applied to protect the surgical wound. This instrument can prohibit skin and subcutaneous tissue damage during surgery. Postoperative subcutaneous negative-pressure drainage is also an effective for avoiding or treating wound disruption.

The transient arm paralysis occurred in the case 7 and 18. They were operated through the fourth ICS and the sixth ICS, respectively. Therefore, the transient paralysis is not considered to be related to the level of thoracotomy. Actually, there were no complications in the patients operated from the seventh to eighth ICS. Currently, a pulse-oxymeter has been applied, on the hand, of the extended arm for monitoring peripheral blood pulse and saturation of oxygen. During operation blood pulse and saturation of oxygen has been kept in normal range. Since then, no patient has experienced transient arm paralysis. Therefore, transient arm paralysis is considered to be vascular origin caused by the hyperextension of arm or the hyperextension of wound.

The surgical field is relatively small; therefore, there are a few technical methods in order to overcome this disadvantage. One-lung ventilation is required for pulmonary lower lobectomy during the dissection of the pulmonary ligament and pulmonary vein. Furthermore, one-lung ventilation provides adequate operative field in ligation of the abnormal artery during surgery of pulmonary sequestration. One-lung ventilation has been technically feasible in infant, using Fogarty embolectomy catheter [7]. Hemoclips facilitate the ligation of pulmonary arteries. The proximal site is ligated by 3-0 or 4-0 silk suture and the distal site is closed by a hemoclip, to provide sufficient distance for a safe cut. A long and fine-tip needle holder and forceps are required for dissection of the TEF and anastomosis of the esophagus in esophageal atresia. Fine monofilament absorbable 5-0 or 6-0 PDS with the two needles in both ends are useful for full thickness stitch suture using an inside-to-outside and inside-to-outside manner.

In conclusions, MSASCI for pediatric thoracic surgery resulted in excellent motor and aesthetic outcomes. MSASCI may become the standard approach for thoracic surgery for the small children, especially for neonates and infants.

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Significance of Abnormalities in Systems Proximal and Distal to the Obstructed Site of Duodenal Atresia

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ABSTRACT

Background: Duodenal atresia (DA) is a well-known neonatal intestinal disease. Even after surgery, the proximal segment can continue to be severely dilated with hypoperistalsis, resulting in intestinal dysmotility problems in later life. No data have been published regarding the morphologic differences between the proximal and distal regions of obstructed sites of the intramural components in DA.

Methods: Operative duodenal samples (N = 12) from cases with DA (age 1–3 days) were used. Age-matched controls (N = 2) were used. All of the specimens were immunohistochemically stained with antibodies to S-100 protein, α-smooth muscle actin, and c-kit protein.

Results: At the proximal segments of the obstructed site in DA, the number of neuronal cells decreased in size and number. The circular musculature was moderately to severely hypertrophic. Unusual ectopic smooth muscle bundles were also identified. The innermost layer of the circular musculature was thinner. Interstitial cells of Cajal are decreased, even around the myenteric plexus. All of the staining in the distal segments in DA was similar to the control tissues.

Conclusions: Proximal and distal segments in DA differ in the neural cells, musculature, and distributions of the interstitial cells of Cajal. Based on the present study, these morphologic changes may contribute to the onset of postoperative duodenal dysmotility.

Key Words: α-smooth muscle actin, duodenal atresia, interstitial cells of Cajal, neural cells

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Duodenal atresia (DA) is a well-known intestinal disease, which frequently causes intestinal obstruction in newborns, and it is commonly associated with other congenital anomalies (1,2). DA accounts for 25% to 40% of all cases with intestinal atresia (IA) (3). The frequency of DA in Japan is reported to be 1 in 3000 to 5000 live births.

Various surgical procedures to anastomose the proximal dilated site to the distal site, such as duodenoduodenostomy and duodenojejunostomy, have been introduced with promising results (4–7). Successful surgical repair has also been reported, with a mortality rate as low as 3% to 5% after correction, in addition to an excellent long-term survival rate (8–10). Even after successful surgery, however, the proximal site can continue to be severely dilated with hypoperistalsis, resulting in intestinal dysmotility problems in later life (11). Dysmotility problems in DA appear to be caused by a dilatation of the intestine proximal to the obstructed site, which has not been adequately resected. Intestinal dysmotility often leads to functional obstruction characterized by marked dilatation resulting from ineffective peristalsis (12–14). These findings have been supported by previous manometric studies, which found a reduction in the intraluminal manometric pressure and a transit disturbance in the dilated proximal intestines (15,16).

Similar to other types of IA, in DA, hyperplasia and hypertrophy of the smooth muscle are found in varying degrees in the proximal site of obstruction, whereas these same conditions are rarely observed at the distal site of the obstruction (17,18). Chick studies have demonstrated several abnormalities in the intramural nervous system, muscular elements, and the interstitial cells of Cajal (ICC) in the proximal dilated segment of the IA. These findings were found not only in human samples of patients with IA but also in a chick IA model (11,19). There are no published data describing the differences between the proximal and distal sections of obstructed sites regarding the intramural components in patients with DA. In the present study, we investigated the morphologic differences in the enteric nervous system, the ICC, and smooth muscle, between the regions proximal and distal to the obstructed site in neonates with DA, to enhance our understanding of motility problems in patients with DA.

METHODS

Tissue Specimens

Twelve resected duodenal samples obtained from neonates with DA who were delivered at Kyushu University Hospital (Fukuoka, Japan) were used in the present study after obtaining the approval of the university ethics committee. The subjects' gestational ages were 34 to 40 weeks, and the duodenal samples were obtained at the primary operation during the subjects' first to third days after birth. The 0.5-cm anterior walls of both the proximal and distal segments apart from the obstructed site were collected as samples. Age-matched duodenal samples of controls were obtained from 2 patients without gastrointestinal disease at an autopsy (congenital diaphragmatic hernia). The number of control material samples was insufficient because of the difficulty in obtaining normal controls for the present study. Formalin-fixed, paraffin-embedded tissues were cut into 4-μm-thick slices and were processed for immunohistochemistry.

Immunohistochemistry

Duodenal specimen slices were stained with hematoxylin and eosin to evaluate the presence of the submucosal and myenteric

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plexus and the smooth muscle layer before performing immunohistochemical staining.

All of the specimens were immunohistochemically stained using the standard avidin-biotin complex method. The primary antibodies were a polyclonal antibody to S-100 protein (code no. 422091 Nichirei Co Ltd, Tokyo, Japan) as a general neuronal marker and an antibody to c-kit protein (CD-117, diluted 1:100; DakoCytomation, Carpinteria, CA) as a marker of ICC, and a monoclonal antibody to α-smooth muscle actin (α-SMA, clone IA4, diluted 1:200; Sigma Immunochemicals, St Louis, MO) as a general muscle marker (Table 1).

In brief, after deparaffinization in xylene and dehydration in 100% alcohol, slides were treated with 3% H_2O_2 in methanol to block endogenous peroxidase activity. For antigen retrieval, the slides were subjected to 10 minutes of microwave treatment in citric acid buffer (pH 6.0). After cooling to room temperature, the slides were incubated with an undiluted blocking solution (Histofine, SAB-PO [MULTI] Kit; Nichirei) containing goat serum albumin. After rinsing with phosphate-buffered saline (PBS), the slides were incubated with a primary antibody (Table 1). The slides were rinsed twice with PBS and incubated for 10 minutes with an undiluted biotinylated secondary antibody (Histofine). Slides were then rinsed again twice with PBS followed by incubation for 10 minutes with undiluted peroxidase-conjugated streptavidin (Histofine). In all of the duodenal specimens stained, peroxidase was detected by diaminobenzidine tetrahydrochloride (Histofine, DAB Kit, Nichirei) with purified water for 5 minutes. Finally, the slides were rinsed with running tap water and counterstained with hematoxylin, dehydrated through a graded alcohol series, and washed with xylene.

Evaluation and Analysis

The morphologic differences were evaluated among the proximal and distal segments of the obstructed sites of DA samples and compared with those of the controls. In addition, the differences between the segments were quantitatively presented. For quantitative evaluation, all of the sections were photographed using light microscopy using 4×, 10×, 20×, and 40× magnifications. The quantification of the immunoreactivities of c-kit were evaluated from each slide by measuring the length of the c-kit-positive area, and the immunoreactivities of S-100 were evaluated from each slice by measuring the length of each stained ganglion or plexus. The α-SMA antibody immunoreactivities were quantified by measuring the thickness of the longitudinal muscle layer, the circular muscle layer, and the muscularis mucosae in 3 different locations. The mean values of the 3 area measurements are presented in Results. All of the measurements were taken using the ImageJ version 1.43s software program (National Institutes of Health, Bethesda, MD) in an area 4080 × 3072 pixels wide, and then were converted to micrometers according to each magnification. The differences between the c-kit-positive area, the length of the neuronal cells, and the width of the mucosal muscle layers of the proximal and distal segments were compared using the Student t test. Differences between the width of the circular muscle layer and the longitudinal muscle layer of the proximal and distal segments were compared using the Mann-Whitney U test. $P < 0.05$ were considered to be statistically significant. All of the statistical analyses were performed with the SPSS statistical software program (SPSS Inc, Chicago, IL).

RESULTS

The present study included 9 patients with type III and 3 patients with type I DA. All of the patients had been antenatally diagnosed as having DA during the prenatal period; therefore, all of the patients were treated in our department after the immediate diagnosis for the confirmation of DA following birth. In all of the patients, a longitudinal incision and a transverse duodenoduodenostomy (diamond-shape anastomosis) or membranous resection was performed 1 to 3 days after birth.

S-100 Protein Staining

In the control samples, immunoreactivity to S-100 antibody was observed in the myenteric, submucosal plexuses, and nerve fibers distributed throughout the entire bowel wall layers. Auerbach plexus between the circular and longitudinal muscle layers was clearly labeled by S-100 protein immunostaining. Several positive fibers were also detected in the muscularis mucosae and in the villus of the lamina propria (data not shown). In the proximal segment of the obstructed sites in the cases with DA, an abnormal nervous distribution showing S-100-positive immunoreactivity was observed (Fig. 1A, B). In the myenteric plexus, the number and size of the S-100-positive plexus were smaller than those in the distal segments and the controls. In addition, a small number of ganglion cells were also observed. The ganglion cells were small and immature compared with those of the distal segments and the controls. Nerve fibers observed between the circular and the longitudinal musculature not only were fewer in number but also were composed of smaller fibers. The size and length of the ganglionic cells were also smaller than those of the distal segments and the controls, especially in the area where hypertrophic musculature was observed (Fig. 1A, B). In contrast, the nervous distribution of the distal segment of obstructed site was undistinguishable from those of controls (Fig. 1C, D). Quantitative analyses showed a significantly shorter ganglion length and plexus of the proximal segments than was observed in the distal segments of the obstructed site (proximal 203.43 ± 103.49 μm, distal 297.67 ± 136.58 μm, $P = 0.002$, Table 2). There was no significant difference in the length of the ganglion and myenteric plexus between the distal segments of the obstructed site and control tissues ($P = 0.134$).

TABLE 1. Antibodies used to evaluate the nervous system, ICC, and smooth muscle layers

Antibody	Code no./clone no.	Species	Dilution	Manufacturer	Marker
S-100	422091	Rabbit polyclonal	5 μg/mL	Nichirei Co Ltd, Tokyo, Japan	Ganglion cells and nerve fiber
α-Smooth muscle actin	1A4	Mouse monoclonal	1:200	Sigma Immunochemicals, St Louis, MO	Smooth muscle cells
c-kit	CD-117	Rabbit polyclonal	1:100	DakoCytomation, Carpinteria, CA	ICC

ICC = interstitial cells of Cajal.

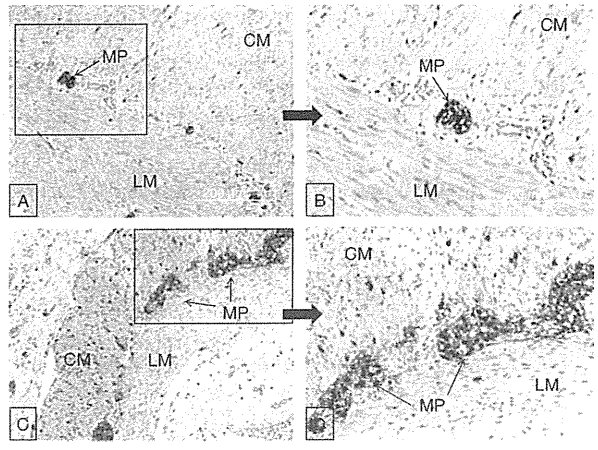

FIGURE 1. The duodenum shows the distribution of S-100 immunoreactive nerve cells and nerve fibers (original magnification 10×, 20×). A, B, The proximal segment of obstructed site of patients with duodenal atresia. The myenteric plexus (MP) was markedly reduced in size and distribution and also contained hypoplastic cells. C, D, The segment distal to the obstructed site in a sample of patients with duodenal atresia. The distribution pattern of the positive nerve cell end fibers is nearly identical to the control samples. CM = circular musculature; LM = longitudinal musculature.

α-SMA Staining

In the control samples, a homogenous immunoreactivity to the α-SMA antibody was observed in all of the muscle layers: the muscularis mucosae, circular muscle layer, and the longitudinal muscle layers (data not shown). In the proximal segment of the obstructed site in samples of patients with DA, a moderately to severely hypertrophic area was observed in the circular and longitudinal muscle layers, particularly in the circular muscle layers, compared with those of the distal segments or the controls (Fig. 2A, B, C). The innermost layer of the circular muscle layer in the proximal segments was also thinner and was nearly undetectable in some sections, compared with those in the distal segments or the controls. In addition, in all of the patients, unusual ectopic muscle bundles were found around the submucosal connective tissue near the innermost layer of the circular muscle layers (Fig. 2B). These smooth muscle bundles originated from the muscle bundle in the thin innermost circular muscle layer. In addition, the muscularis mucosae were also found to be hypertrophic (Fig. 2C). In contrast, in the distal segments of the obstructed site in DA, the staining pattern of α-SMA antibody was similar to that observed in the control samples (Fig. 2D, E, F). There was no significant difference in quantitative analyses of the thickness of the circular muscle layers, the longitudinal muscle layers, and the muscularis mucosae between the distal segments of obstructed sites and control tissues ($P = 0.646$, $P = 598$, and $P = 0.395$, respectively). In contrast, quantitative analyses revealed a significant difference in the thickness of the muscularis mucosae of the proximal segments compared with the distal segments of the obstructed site (proximal 36.46 ± 13.51 μm, distal 12.52 ± 6.06 μm, $P < 0.001$, Table 2). Quantitative analyses also revealed a significant difference between the circular muscle layers of the proximal and distal segments of the obstructed site (proximal 492.91 μm [range 263.19–733.16 μm], distal 164.94 μm [range 135.61–199.37 μm], $P < 0.001$, Table 2). There was also a significant difference between the proximal and distal segments of the longitudinal muscle layers (proximal 317.64 μm [range 110.73–369.18 μm], distal 96.28 μm [range 73.83–121.20 μm], $P < 0.001$, Table 2).

C-kit Staining

In the control samples, c-kit-positive cells were observed between the intermuscular space of the circular and longitudinal muscle layers, particularly around Auerbach plexus (data not shown). A small number of positive cells also were localized to the circular and longitudinal muscle layers and in the innermost layer of the circular muscle layers. In the proximal segment, the number of c-kit-positive cells was markedly decreased (Fig. 3A, B). Moreover, in some samples, the ICC were barely detectable, even around the myenteric plexus. The positive cells were bipolar in shape. Macrophage-like cells positive for c-kit staining were also observed within the muscularis propria and the submucosal area. Unlike the proximal segments, the distribution pattern and c-kit immunoreactivity in the ICC of the segment distal to the obstructed site were similar to those of the control samples (Fig. 3C, D; $P = 0.133$). These cells formed a network with cell-cell contacts and their shape was multipolar. The quantitative analyses revealed a significantly smaller c-kit-positive area in the proximal segments compared with the distal segments of the obstructed site (proximal 933.45 $\mu m^2/mm^2$ [range 297.87–3149.62 $\mu m^2/mm^2$], distal 12006.42 $\mu m^2/mm^2$ [range 2473.79–22458.1 $\mu m^2/mm^2$], $P < 0.001$, Table 2).

DISCUSSION

As a part of the normal growth process in the embryo from the fourth to the seventh week of gestation (embryo length 8.6–14.5 mm), the epithelial cells of the duodenum begin to proliferate

TABLE 2. Imunoreactivity comparison of the c-kit protein, S-100 protein, and α-smooth muscle actin antibody staining in the proximal and distal segments of obstructed site in samples of patients with duodenal atresia

	Proximal to obstructed site	Distal to obstructed site	*P*	Normal control
Nervous system (length/field)	203.43 μm (103.49)	297.67 μm (136.58)	0.002	373.27 μm (143.09)
Circular muscles layers thickness	492.91 μm (263.19–733.16)	164.94 μm (135.61–199.37)	<0.001	158.91 μm (34.07)
Longitudinal muscle layers thickness	317.64 μm (110.73–369.18)	96.28 μm (73.83–121.20)	<0.001	106.54 μm (13.34)
Muscularis mucosae thickness	36.46 μm (13.51)	12.52 μm (6.06)	<0.001	14.92 μm (2.89)
ICC positive area, $\mu m^2/mm^2$	933.45 $\mu m^2/mm^2$ (297.87–3149.62)	12,006.42 $\mu m^2/mm^2$ (2473.79–22,458.1)	<0.001	20,717.36 $\mu m^2/mm^2$ (5925.64)

Data are presented as mean (SD); median (25%–75%). ICC = interstitial cells of Cajal; SD = standard deviation.

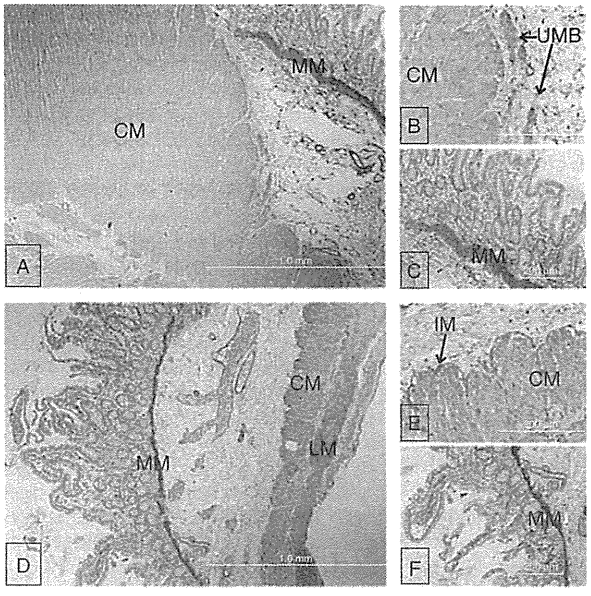

FIGURE 2. The duodenum shows the distribution of immunoreactivity to α-smooth muscle actin antibody (original magnification 4× and 20×). A, B, C, The segment proximal to the obstructed site in a sample of patients with duodenal atresia. The circular musculature (CM) is moderately to severely hypertrophic. Unusual muscle bundles (UMB) with an oblique configuration were observed in the submucosal area, and the muscularis mucosae (MM) were hypertrophic. D, E, F, The distal segment of the obstructed site in a sample of patients with duodenal atresia. The lamina propria, the MM, the innermost layer of circular musculature (IM), and the longitudinal musculature (LM) are immunolabeled for α-smooth muscle actin antibody and are similar to those of the controls.

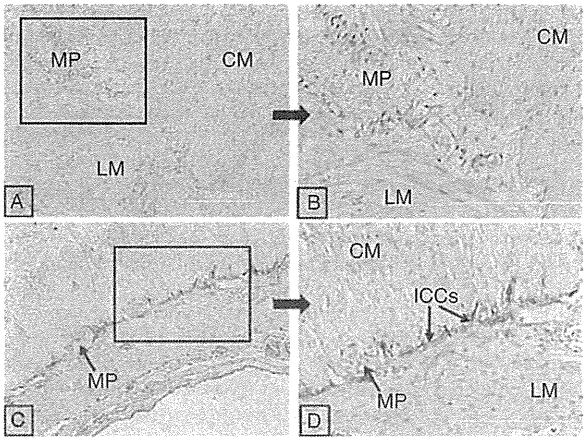

FIGURE 3. The duodenum showed the distribution of immunoreactivity to c-kit antibody (original magnification 10× and 20×). A, B, The proximal segment of the obstructed site in a sample of patients with duodenal atresia. There were few or no positive cells around the myenteric plexus (MP). C, D, The distal segment of the obstructed site in a sample of patients with duodenal atresia. Numerous positive cells were located around the MP, and a few positive cells were also distributed in the intermuscular space of the circular musculature (CM). LM = longitudinal musculature; ICC = interstitial cells of Cajal.

and completely plug the lumen (solid phase). Therefore, between the 15- and 65-mm stages (from the end of the 7th week to the 12th week of gestation), a process of vacuolization, coalescence of vacuoles, and recanalization occurs. DAs, stenosis, and intraluminal webs are believed to be caused by insults resulting in recanalization failure during the lengthening and rotation of the primitive foregut. A resultant obstruction is then believed to cause the dilatation in the proximal duodenum (20–22).

Using histochemical techniques, we have herein provided the first study of the potential differences in abnormalities of the smooth muscle, nervous system, and ICC between the segments proximal and distal to the obstructed site in samples from patients with DA. These 3 enteric components, which are involved in peristaltic activity, were immunohistochemically analyzed.

Although the etiology of DA is not the same as that in other IAs, the morphologic changes of the intestine in DA are thought to be similar. The morphologic change of the proximal segment seems to depend on the postobstructive dilatation during the fetal period. Similarly, in other forms of IA, morphologic change in the proximal segments also depends on the change after the formation of the obstruction.

In an experimental model of IA, several studies showed that the dilatation of the proximal segment induces the involution and lysis of the ganglion cells after initial hyperplasia of the myenteric ganglia has occurred and irreversible distension continues to develop (23). Another possible cause of nerve alteration could be ischemic influence during fetal life through vascular disruption as shown in IA models (19,23). In the present study, we observed that in the area in which muscular layers are severely dilated, the distribution of ganglion and plexus is also less than that of the area with moderately dilated muscular layers. This finding supported a previous IA study (19), which observed marked abnormal neuronal changes in the distended proximal segments. In contrast, the neuronal distribution in the distal segment was close to normal in these studies, as in our study of human DA. The influence of muscular distention on the neuronal cell alteration is also shown in our previous case report of IA (24). In this case report, an improvement in numbers of neuronal cells and fiber distribution between primary operation of IA at 2 days after birth and second operation for the reconstruction of the dilated proximal segment at 6 months of age was observed (24). These abnormalities are probably a result of the developmental delay in the nervous system or of the dilatation of the proximal segment in DA, as mentioned in IA studies, which also found an alteration of enteric nerves in a severely dilated area of the proximal segment (11).

When examining smooth muscle morphology in the present study, we observed that the muscle layers in the proximal segments of the obstructed site are moderately to severely hypertrophic, unlike in the distal segments, which are indistinguishable from those of the control samples. This muscular hypertrophy has been well documented and results from a compensatory process following obstruction during the prenatal period, and it is localized exclusively to the circular musculature of the distended proximal intestinal segment (23,25,26). As mentioned in the literature, dysmotility of the intestine is often encountered in a severely dilated muscle of the segment proximal to the obstructed site. To prevent recurrence of the dilated segment, the markedly dilated

duodenum must be completely reconstructed surgically. Even after reconstruction surgery, however, a proximal segment consisting of a hypertrophic area remains because of the difficulty in visualizing the healthy area and minimizing the resected segment. Previous investigators have shown that the contractile pressure in the dilated proximal intestine of an IA model is lower than that in normal intestines. Moreover, physiologic studies of humans and animal models of IA have also shown a decrease in the motor activity in both the proximal and distal segments. These studies suggest that low contractile pressure was involved in the postoperative dysmotility (17). In addition, the existence of unusual muscle bundles, which have an oblique configuration, likely contributes to the disturbed bowel rhythms. Similar findings have been described in our previous study of cases with IA (17). Therefore, the existence of both hypertrophy of the circular muscle layers and unusual muscle bundles in the submucosal layers likely contributes to the development of motility disorders later in life, even after a successful initial operation. Additional procedures, such as intestinal plication or tapering the dilated intestine, are sometimes needed to produce efficient peristalsis of the proximal intestines.

Of particular interest with regard to the occurrence of unusual muscle bundles, our previous study of human IA showed that the smooth muscle bundles which emerged from the innermost layer of the circular musculature could be of either an oblique or vertical orientation to the long axis of the intestines, stretching toward mucosae, forming a coarse, irregular meshwork in the submucosa (17). Based on the chronologic view of our previous study of myogenesis in chick embryos, it is supposed that these muscle bundles may be a remnant of early developmental stages during the formation of the muscularis mucosae (27). Another study also proposed that a possible explanation for this phenomenon is that the ectopic muscle bundles are a secondary reaction of muscle cells to the chronic and progressive dilatation of the proximal segments. Moreover, these bundles also could indicate a secondary regressive reaction, which the proliferating reaction of regressive smooth muscle cells undergo when they first emerge in the inner layer of the circular muscle layer; thereafter, these smooth muscle cells protrude from the inner layer of the circular muscle layer to the layer of muscularis mucosae, according to the rules of normal development. The real causality regarding the development of ectopic muscle bundles in the proximal segment of the DA remains unclear, and the proposed reasons are based mostly on experimental IA, which is probably not appropriate for DA because of differences in the underlying etiology (27,28).

The small intestine exhibits rhythmic and phasic contractions that form the basis for propagating and segmental contraction. These rhythmic and phasic contractions are generated by the ICC surrounding the myenteric plexus (ICC-MY) between the longitudinal and circular muscular layers and the ICC lining the septa separating the CM bundles (ICC-SEP). Each ICC-MY and ICC-SEP generate a spontaneous electrical slow-wave pacemaker activity that is actively propagated through the ICC network, in addition to regulating smooth muscle membrane potential and mediating enteric neurotransmission. The loss or abnormalities of ICC have been described in a variety of human motility disorders, including hypoganglionosis, Hirschsprung disease, and jejunal and ileal atresia but not in DA (29–31). A reduction in the distribution of pacemaking cells has also been reported in a dilated colon of 2 neonates with atresia of the colon (32). In the present study, we observed that the proximal segments of the obstructed site showed not only a decreased immunoreactivity to c-kit protein but also a markedly reduction in the number of ICC. The distribution of ICC also showed a discrete distribution without connection of ICC cells and a bipolar shape. This finding may be associated with the reduction of pacemaker activity and enteric neurotransmission, thus resulting in hypoperistalsis of the proximal segments. Several physiologic studies also showed that peristalsis and spontaneous contraction were disturbed in the proximal segments. Therefore, the abnormality of ICC in the proximal segments may lead to postoperative dysmotility in DA.

In the present study, abnormalities of the enteric nerves, smooth muscle cells, and ICC were predominantly observed in the proximal segments. It has been pointed out that a tight connection existed between the ICC, enteric nervous system, and the smooth muscle to produce a synchronized and sustainable contraction of the duodenum (30). Therefore, the observed abnormalities in these 3 enteric components of the proximal duodenum suggest that duodenal motility disorders may occur later in postnatal life.

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ORIGINAL ARTICLE

Therapeutic strategy for persistent cloaca: the efficacy of antegrade continent enema as a salvage surgery

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Abstract
Purpose The aim of this study is to evaluate our therapeutic strategy for persistent cloaca from the viewpoint of long-term functional outcome.
Materials and methods This study covers 17 cases of persistent cloaca treated at our institution and followed for more than 3 years. As a definitive repair for anorectal and urogenital systems, simultaneous surgery with posterior sagittal approach or anorecto-urethrovagino-plasty (PSARUVP) was performed. The length of the common channel and the shape of the vagina determined the vaginoplasty methods. Fecal function was assessed with the scoring system of the Japan Study Group of Anorectal Anomalies.
Results Anorectoplasty was performed with the posterior sagittal approach in 15 cases and with the perineal approach in two. Vaginoplasty was performed with total urogenital mobilization in nine cases, rectal interposition in four, vaginal flap in two and with other methods. Fecal function was classified as good in three cases, moderate in ten, and poor in four. In the poor cases, Malone's antegrade continence enema (MACE) was performed, which improved fecal function significantly.
Conclusion PSARUVP might be the optimal surgery for persistent cloaca at present; however, satisfactory fecal function could not be achieved in those cases with a longer common channel. MACE effectively compensated for the poor outcome and was especially successful at eliminating incontinence.

Keywords Persistent cloaca · Anorectoplasty · Vaginoplasty · Posterior sagittal approach · Anorecto-urethrovagino-plasty · Antegrade continence enema

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Introduction

Definitive repair of persistent cloaca remains a reconstructive challenge for pediatric surgeons and urologists, and no therapeutic strategy for a long common channel has been well established. We have been employing posterior sagittal anorecto-urethrovagino-plasty (PSARUVP) as the primary repair. In order to determine the optimal therapeutic strategy, we reviewed our cases of persistent cloaca and evaluated the therapeutic strategies used. For cases of poor fecal function following PSARUVP, we employed MACE and evaluated the effectiveness of the salvage surgery.

Materials

This study covers 17 female cases of persistent cloaca treated at the Osaka Medical Center and Research Institute for Maternal and Child Health between 1992 and 2006 and followed for more than 3 years. Their ages ranged from 4 to 21 years; the age at operation was between 4 months

Table 1 Clinical fecal function versus length of cloaca

Fecal functions	Score	2–2.5 cm (5 cases)	3–3.5 cm (6 cases)	4 cm (6 cases)	Total (17 cases)
Desire of defecation					
a. Absent	0	0	1	0	1
b. Not always	1	0	1	1	2
c. Always	2	5	4	5	14
Constipation					
a. Unmanageable requiring irrigation or manual extraction of feces	1	1	0	0	1
b. Manageable with daily enema	2	1	5	4	10
c. Better than b and worse than d	3	2	0	2	4
d. No constipation	4	1	1	0	2
Soiling					
a. Daily	0	0	2	0	2
b. More than twice a week	1	1	1	0	2
c. Better than b worse than d	2	0	1	2	3
d. Only with diarrhea	3	2	0	0	2
e. Never	4	2	2	4	8
Staining					
a. Daily	0	0	3	0	3
b. Better than a and worse than c	1	0	1	2	3
c. Never	2	5	2	4	11

The column at left shows the scoring system proposed by the Japan Study Group of Anorectal Anomalies [6]. The column at right shows the individual scores of each cloacal length group

and 5 years, with the average being 1 year 10 months; and the follow-up period was between 3 and 20 years, with the average being 9 years 11 months.

Methods

Individual multidisciplinary therapeutic strategies were devised that included (1) antenatal diagnosis and perinatal care (e.g., vesicoamniotic shunt); (2) respiratory and circulatory care beginning just after birth; (3) decompression of the gastrointestinal tract (e.g., enterostomy); (4) decompression of the urogenital tract (e.g., cystostomy); (5) correction of severe genito-urinary anomalies (e.g., cut-back of phallic urethra); (6) primary repair of anorectal and urogenital tracts; (7) urinary control/training; (8) fecal control/training; and (9) repair/care of gynecological problems. Primary anorectal and urogenital repair were performed simultaneously through the posterior sagittal approach [1]. For vaginoplasty, total urogenital mobilization (TUM) [2] was performed. Rectal interposition [3, 4] was performed when the bifurcation of the vagina and cloaca could not be pulled down to the perineum with TUM. A vaginal flap was employed when the vagina was sufficiently dilated for elongation [5]. Clinical fecal function was assessed with the scoring system of the Japan Study Group of Anorectal Anomalies [6], which comprised a four-item questionnaire: desire for defecation, constipation, incontinence, and staining. These items were scored as 2, 4, 4, and 2, respectively, and the total score was calculated by combining the scores for desire for defecation (perfect score of 2), staining (score of 2), and one of two items with a lower score—either constipation (score of 4) or incontinence (score of 4). A total perfect score is 8 (Table 1). Antegrade continence enema was performed with the appendix in keeping with Malone's report [7], by which antireflux intussusception was fashioned, and Y-appendicoplasty was added to prevent stenosis of the stoma [8].

Results

All cases except one of a common channel exceeding 3 cm and one case of a common channel less than 3 cm, or 10 cases out of 17 (59%), were diagnosed antenatally through ultrasonography. The most common findings included hydrocolpos or hydrometrocolpos in eight cases; hydronephrosis or hydroureter in seven; ascites and oligohydramnios in five each; intestinal dilatation and meconium peritonitis in two each; and hydrops in one. Prenatal intervention was performed in four cases; vesicoamniotic shunt placement in one for megacystis with oligohydramnios at 16th weeks of gestation; and early induced delivery in three for progressive hydronephrosis at 30–32 weeks of gestation. Eventually, their renal function was maintained. As for decompression of the gastrointestinal tract, enterostomy

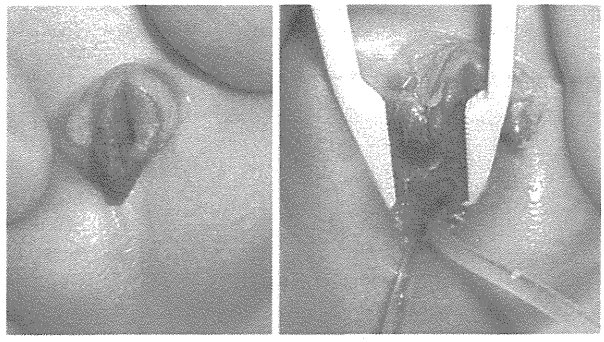

Fig. 1 Phallic urethra cut-back procedure. Phallic urethra is typical of persistent cloaca (*left*). Following the cut-back procedure on the phallic urethra, the cloacal orifice is exposed at the physiologic position (*right*). The length of the common channel as measured via cystoscopy after the incision is approximately 1.5 cm shorter than the measurement obtained via the contrast study

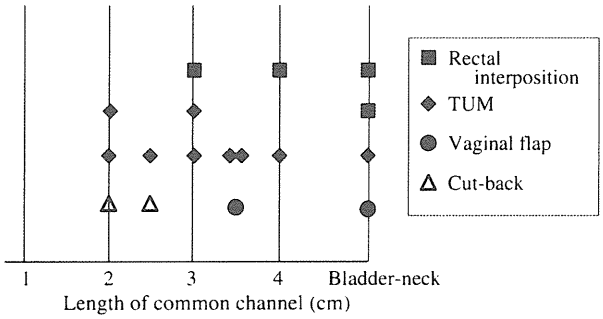

Fig. 2 Length of common channel versus type of vaginoplasty. TUM was employed as the primary form of vaginoplasty. When the confluence of the vagina could not be pulled down to the perineum with TUM, rectal interposition was performed. In cases of dilated vagina, the vaginal flap procedure was employed

was performed within 1 day of birth in all cases. As for decompression of the urinary tract, cystostomy was performed in six cases, vaginostomy in three, and clean intermittent vaginal catheterization in eight. As for primary reconstruction of the anorectal system, posterior sagittal PSARUVP was performed with an abdominal approach in 14 cases, with a posterior sagittal anorectoplasty (PSARP) in two and with a solely perineal approach in one. As for primary vaginal reconstruction, TUM was performed in nine cases, rectal interposition in four, vaginal flap in two, and cut-back of phallic urethra alone in two (Figs. 1, 2).

The Table and Fig. 3 show the fecal function assessed at 3 years or later following definitive surgery employing the scoring system. Desire was rated "good" regardless of the length of cloaca and "absent" in only one case (6%); constipation was rated "not good," with 11 cases (65%) requiring daily enema or more aggressive therapy; incontinence was rated "not good," with 7 cases (41%) reporting daily or occasional incontinence, even without diarrhea; and

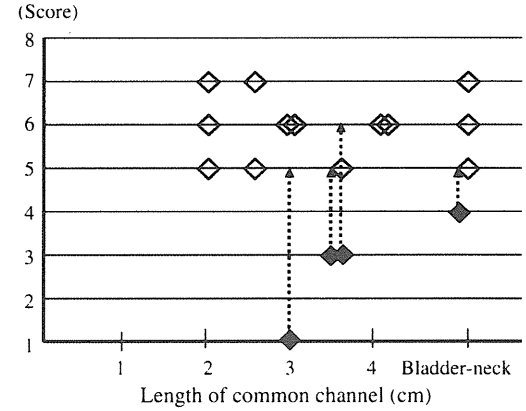

Fig. 3 Length of common channel versus continence score. Although no clear correlation exists between the score and the length of the common channel, the length in cases associated with a poor score (*closed square*) was 3 cm or greater. Following the adoption of MACE with daily antegrade enema, the scores rose to 5 and 6 (*dotted arrows*) because both incontinence and staining were completely eliminated, only the score for sensation remained unchanged

staining was rated relatively good, with three cases (18%) reporting daily staining (Table 1). The total score was classified as "good" (score of 7–8) in three cases; "moderate" (score of 5–6) in ten cases; and "poor" (score of 4 or less) in four cases (Fig. 3). Although no clear correlation existed between the scores, in the four cases with poor scores, the length of cloaca was 3 cm or greater (Fig. 3). In these four cases, Malone's antegrade continent enema (MACE) was performed. Following MACE with daily antegrade enema, both incontinence and staining were eliminated, with only the score for sensation remaining unchanged, thus increasing the scores to 5 and 6 (Fig. 3). Regarding urinary function, 13 (76%) achieved continence, although 11 required CIC. Ten of the 12 cases (83%) that underwent urodynamic study maintained good compliance. Some of the data were reported in the literature [9]. All eight cases of 12 years old and older began menstruation. Three of them presented with dysmenorrhea just after menarche because of duplex uterus; in these earlier cases, one of the duplex uteri was not drained at the time of definitive surgery.

Discussion

With the increasing incidence of antenatal diagnosis of congenital anomalies, the percentage of cases of antenatal diagnosis of persistent cloaca has been increasing, reaching 59% of the presented series. Therefore, therapeutic strategy should include perinatal treatment, such as vesicoamniotic shunt or induced delivery, to ensure good long-term urinary and renal function. For persistent cloaca, simultaneous repair of the anorectal and urogenital systems with the

posterior sagittal approach might be the optimal, and one of the most common, procedures at present [10, 11]. However, the fecal function is not always satisfactory. The factors responsible for the poor outcome include sacral deformity concomitant with abnormal innervation, underdeveloped pelvic muscles, and a longer common channel [11]. For the abnormal innervation and underdevelopment, pediatric surgeons can only pull down the rectum through the center of the pelvic muscle as precisely as possible with minimally invasive surgery. The posterior sagittal approach is likely the optimal method at present; however, the laparoscopically assisted procedure might result in a better pull-through route as a form of surgery that is even less invasive [12, 13]. As Pena emphasizes, the length of the common channel, at 3 cm, is the most important determinant of the therapeutic strategy, in addition to the requirement for highly capable pediatric urologists, for long-term fecal and urinary function. He suggested measuring the length with diagnostic cystoscopy and vaginoscopy [11]. We used to measure this length with a contrast study between the urinary outlet and the bifurcation of the vagina. Recently, however, we have been performing a cutback procedure, or incision of the phallic urethra, to expose the real cloacal orifice during the neonatal period, usually with a colostomy. We then measure the length with cystoscopy and vaginoscopy, not with a contrast study, in order to diagnose the type of disease precisely. The common channel as measured with endoscopy is approximately 1.5 cm shorter than that as measured with a contrast study. In this series, the poor correlation between the length and the antenatal diagnostic ratio, therapeutic strategy, and fecal function might be partially attributable to the difference in measuring methods in earlier cases.

In the present series and in the series reported by Pena, satisfactory fecal function could not be achieved in some cases, especially those with a longer common channel, even with an optimal repair. The authors applied antegrade continent enema, MACE, for intractable constipation with overflow incontinence. With MACE, the patients were rendered completely free from incontinence and staining. Thus, the authors conclude that antegrade continent enema is valuable as a salvage surgery after definitive surgery for persistent cloaca with poor fecal function.

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Psychosocial and cognitive consequences of major neonatal surgery

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Key words:
Major neonatal surgery;
Child behavior checklist;
Psychosocial consequence;
Cognitive assessment;
Quality of life;
Long-term follow-up

Abstract

Purpose: To evaluate the long-term quality of life (QOL) of patients who had undergone major neonatal surgery, the psychosocial and cognitive consequences of neonatal surgical stress were assessed when the patients reached school age.

Materials and methods: Seventy-two patients who had undergone major neonatal surgery were enrolled in this study. Their primary diseases were anorectal malformation (ARM) in 27 cases, esophageal atresia (EA) in 23, and congenital diaphragmatic hernia (CDH) in 22. Intelligence tests using Wechsler Intelligence Scale for Children III (WISC-III) or a developmental test and the Child Behavior Checklist were conducted through questionnaires and interviews with clinical psychologists.

Results: Mental retardation (MR) was apparent in 25% of EA, 20% of ARM, and 18% of CDH, significantly higher than the 2% to 3% commonly found in the general population. The clinical range (CR) of the Child Behavior Checklist was seen in 35% of EA, 59% of ARM, and 38% of CDH, which is also significantly higher than the 25% typically seen in the general population. No significant differences in MR and CR were seen among the primary diseases. The most important factors influencing MR and CR remain to be identified.

Conclusions: To ensure true quality of life after neonatal surgical stress, pediatric surgeons must consider not only physical assessments but also cognitive, emotional, and psychosocial assessments.

Pediatric surgeons sometimes notice emotional problems in patients who have undergone major surgery early in their lives, even among those who exhibit sound physical and mental development. Pediatric surgeons do not generally

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recognize that their patients' psychosocial impairment is deeply associated with the disease or surgical stress they themselves were involved in. To ensure the long-term quality of life of those patients who underwent major surgery during the neonatal period or in early infancy, pediatric surgeons should be aware of the long-term psychosocial and cognitive effects of neonatal surgical stress.

On the other hand, the clinical outcomes of neonatal surgery have been most commonly assessed by survival rate and functional achievement. Recently, more attention has been paid to the effects of neonatal surgical stress on mental and intellectual development. However, the long-term psychosocial and cognitive consequences of neonatal surgical stress have not been extensively documented [1,2], if at all, or only for certain diseases, specifically anorectal malformation (ARM) [3-6] and Hirschsprung disease [7-9].

1. Material and methods

Seventy-two pediatric patients above school age, 37 males and 35 females, all of whom had undergone major surgery during the neonatal period or in early infancy, were enrolled in this study. Their ages ranged between 6 and 17 years. The subjects of the study included the most typical neonatal surgical diseases requiring long-term follow-up: esophageal atresia (EA) in 23 cases, high and intermediate types of ARM in 27, and congenital diaphragmatic hernia (CDH) in 22. The index patients were divided into 2 groups according to hospital stay: Gr. S for a hospital stay of less than 60 days (n =37) or Gr. L for a stay of more than 60 days (n =35). They were also divided into 2 additional groups according to the number of surgeries: Gr. O for 1 surgery (n =20) or Gr. T for 2 or more (n =52).

1.1. Surgical stresses

To evaluate the surgical stress, for example, length of hospital stay, number of surgeries, exposure to life-threatening episode (LTE), and home medical treatment (HMT), pediatric surgeons reviewed the medical records. Life-threatening episode was defined as neonatal asphyxia, resuscitation with mechanical ventilation, cardiac massage, or administration of nitric oxide or catecholamine. Home medical treatment after discharge included oxygen inhalation, mechanical ventilation, parenteral nutrition, enteral nutrition, and intermittent catheterization.

1.2. Intelligence tests and developmental tests

To assess cognitive ability, the subject was given an intelligence test using WISC-III [10]; those unable to take WISC-III took a developmental test [11]. These tests were administered in 67 cases. Sixty-seven of the 72—20 in EA, 25 in ARM, and 22 in CDH—were administered both intelligence tests and developmental tests. Mental retardation (MR) was defined as an IQ of less than 70.

1.3. Child Behavior Checklist

For comprehensive evaluation of emotional and behavioral problems, the parents completed the Child Behavior Checklist (CBCL) and questionnaires through interviews with clinical psychologists. The CBCL used the internalizing T score (ITS, comprising social withdrawal, somatic complaints, and anxiousness/depression), externalizing T score (ETS, comprising delinquent behavior and aggressive behavior), and total summary score (TSS, comprising 3 items of ITS and 2 items of ETS plus social problems, thought problems, and attention problems) [12,13]. The CBCL was completed in 71 cases. The clinical range (CR) of the CBCL was defined as a score of at least 60 for 2 or more of ITS, ETS, and TSS [14].

1.4. Statistical analysis, ethical committee

The study was approved by the ethical committee of the hospital (no. 342). The data were analyzed with the χ^2 test and the Fisher's Exact test. $P < .05$ was considered significant.

2. Results

Mental retardation was recognized in 14 cases in total (67): 5 cases of EA (20), 5 of ARM (25), and 4 of CDH (22) (Table 1). Although the incidence of MR did not differ

Table 1 Prevalence of MR

Diseases (case no.)	EA (20)	ARM (25)	CDH (22)	Total (67)	*P*
MR cases	5 (25%)	5 (20%)	4 (18%)	14 (21%)	NS
Groups (case no.)	Gr. S (34)	Gr. L (33)	Total (67)		*P*
MR cases	4 (12%)	10 (30%)	14 (21%)		NS
Groups (case no.)	Gr. O (18)	Gr. T (49)	Total (67)		*P*
MR cases	2 (11%)	12 (24%)	14 (21%)		NS

NS indicates not significant.

among the primary diseases, that in each study group was significantly higher than the 2% to 3% commonly found in the general population [10,11]. Mental retardation was recognized in 4 cases of Gr. S (34) and in 10 cases of Gr. L (33), for an incidence of 12% and 30%, respectively. The incidence of MR in Gr. L was higher than that in Gr. S; however, no statistical significance between the 2 groups was found. Mental retardation was recognized in 2 cases of Gr. O (18) and 12 cases of Gr. T (49). The incidence of MR in Gr. T was higher than that in Gr. O; however, no statistical significance between them was found.

The CR of the CBCL was seen in 32 cases in total (71); 8 cases of EA (23), 16 of ARM (27), and 8 of CDH (21) (Table 2). Although no significant difference was seen in the prevalence of the CR among the primary diseases, the prevalence in each study group was significantly higher than the 25% typically seen in the general population ($P < .001$) [13]. The CR was noted in 17 cases of Gr. S (36) and 15 of Gr. L (35), for a total of 27 cases (71), representing an incidence of 47% and 43%, respectively; no difference was evident between these 2 groups. The CR of CBCL was noted in 6 cases of Gr. O (20) and 26 of Gr. T (51); the prevalence of the CR in Gr. T seemed higher than that in Gr. T, and there was no significant difference between these 2 groups.

The CR was noted in 18 of the cases with LTE (41) and 6 of those without LTE (9) and in 8 of the cases with HTM (17) and 24 of those without HMT (54); consequently, no difference was evident in the prevalence of the CR between cases with and without LTE and between cases with and without HMT.

To eliminate the effect of MR on the CBCL, the prevalence of the CR in cases of an IQ exceeding 80, or cases of normal intelligence, was calculated. The CR was seen in 5 (42%) of 12 cases of EA, 8 (47%) of 17 cases of ARM, and 6 (40%) of 15 cases of CDH, which did not differ from the prevalence seen in the total of all cases.

3. Discussion

We pediatric surgeons sometimes notice that patients who have undergone major surgery during the neonatal period or in early infancy have emotional disturbances or interpersonal-relationship disorders. Unlike neurologically impaired patients, however, these conditions are not recognized as a consequence of neonatal surgical stress or as being secondary to the diseases per se, and they are not considered for treatment or handled as disorders. To determine the actual incidence of psychosocial and cognitive consequences in patients after major neonatal surgery, the authors conducted this study in cooperation with clinical psychologists.

The incidence of MR was discovered to be unexpectedly high in the study group and much higher than that found not only in the general population but also in the control group and in the extremely low birth weigh patients who had undergone minor surgery. None of the subjects had an ischemic or hypoxic episode during the perinatal or perioperative periods or experienced an LTE after one or more surgeries. The kind of primary disease, length of the hospital stay, and number of surgeries were not responsible for the etiology of MR. Ludman et al [2] reported that those patients who had undergone major neonatal surgery were lagging significantly in educational attainment regardless of the type of disease. They did not identify any risk factors, except for mechanical ventilation, as being responsible for the poor educational attainment in early adolescence. Although the cause of the high incidence of MR was not identified in this study, major surgical stress during the neonatal period, subsequent persistent medical problems, or insufficient early child care might be involved in the etiology of MR. For prevention or early intervention, a more meticulous analysis of their history not only during hospital stay but also after discharge would be indispensable for identifying the real risk factors for MR.

In this study, the authors focused on the psychosocial effects of major surgical stress during the neonatal period and subsequent persistent medical problems in school-aged children. We undertook this study because even mentally healthy subjects showed almost the same incidence of emotional and psychosocial impairment regardless of the type of disease. Some reports indicate that poor fecal continence after surgically corrected ARM [4,5] and Hirschsprung disease [7,8] resulted in poor QOL and more

Table 2 Prevalence of clinical range on CBCL

Diseases (case no.)	EA (23)	ARM (27)	CDH (21)	Total (71)	*P*
CR cases	8 (35%)	16 (59%)	8 (38%)	32 (45%)	NS
Groups (case no.)	Gr. S (36)	Gr. L (35)	Total (71)		*P*
CR cases	17 (47%)	15 (43%)	32 (45%)		NS
Groups (case no/)	Gr. O (20)	Gr. T (51)	Total (71)		*P*
CR cases	6 (30%)	26 (51%)	32 (45%)		NS

NS indicates not significant.

behavioral problems in school-age patients. They supposed that continence dysfunction and anally invasive treatment were responsible for the psychosocial consequences. However, Ludman et al [9] and Ojmyr-Joelsson et al [6] reported that their patients with ARM did not experience psychosocial impairment despite significant functional problems and chronic illness. In our study, the CR was equally prevalent in different types of major surgical stress regardless of persistent medical problems, which suggests that fecal dysfunction in ARM cases affects psychosocial outcome significantly. Although the risk factors for impaired psychosocial consequences after major neonatal surgery remain to be clarified, pediatric surgeons must concern themselves with the long-term effects of neonatal surgical stress on emotional and psychosocial health to improve their patients' long-term quality of life after neonatal surgery.

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A preliminary report on the significance of excessively long segment congenital hypoganglionosis management during early infancy

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Abstract

Background/Purpose: Excessively long segment of congenital hypoganglionosis is rare, and therapeutic strategies to treat this disorder are not well established. The purpose of this study is to describe the significance of management in the neonatal and early infancy period.

Patients and Methods: Four patients (aged 1-4 years) with hypoganglionosis were selected for this study, of which 3 were treated at our hospital. In the initial treatment of 3 cases, an intraoperative pathological diagnosis was made on the basis of findings from simultaneous biopsies taken from the jejunum and sigmoid colon. Retrospective reviews of these patients were performed.

Results: Initial double-barrel jejunostomy at less than 50 cm from the ligament of Treitz allowed patients to start oral nutrition within a week following surgery. Subsequent refashioning of the initial jejunostomy to the Bishop-Koop type was performed at 3 to 6 months of age. Intravenous hyperalimentation was required to meet less than 50% of nutritional requirements, and patients were able to maintain their body weight within 1.5 SD of the normal mean body weight. Liver function test results were also within normal limits in the 3 patients treated at our hospital.

Conclusion: Early diagnosis and treatment may help improve the management of patients in the early stages of hypoganglionosis.

1. Background/purpose

Hypoganglionosis was previously not considered as an isolated entity [1], but recent research has led to it being defined as a 40% reduction in the number of nerve cells in the bowel wall. In addition to 3 forms of moderate hypoganglionosis associated with chronic constipation [2] and an acquired form of hypoganglionosis [3], an excessively long segment of congenital severe hypoganglionosis has been described. The latter is a rare disorder and has a poor prognosis [4], and there are no well-established therapeutic strategies for its management. Okamoto et al [5] collected 16 patients reporting excessively long segment of congenital hypoganglionosis from 1970 to 1993. Out of the 16 patients, 11 patients maintained their nutrition totally parenterally.

Hypoganglionosis is a disease characterized by severe malnutrition and liver dysfunction, often needing multiple surgeries, with some patients requiring small bowel

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transplantation in early infancy. Previous reports have described that, in most cases, the recreation of an ostomy in proximal intestinal segments is required [3] because of dysfunction of the initial stoma. This study aims to address the simplified diagnostic features and management of this type of congenital hypoganglionosis using a recently devised 2-stage surgical technique.

2. Patients and methods

Seven patients (aged 1-20 years) with excessively long segment congenital hypoganglionosis characterized by intestinal dysmotility had been treated in our hospital for the last 4 years. Three patients (aged 9-20 years) were excluded from the study because they were admitted in late childhood and had previously been extensively treated during early infancy at other hospitals. Of the patients treated during early infancy in our hospital, 3 (patients 2-4) were initially treated at our hospital, whereas one was treated at another hospital (patient 1). Patient 1 was diagnosed with hypoganglionosis from multiple biopsies of the jejunum, ileum, and colon in the department of pathology at an alternate hospital. The diagnosis of hypoganglionosis in patients 2 to 4 was made based on histopathological examination of full-thickness biopsies from the jejunal and sigmoid colon that were performed during the initial surgery. The histological diagnosis in patients 2 to 4 was reconfirmed by an independent pathologist in the Department of Pathology from Nagoya University Hospital. The entire circumference of the jejunal segment was obtained at the resected site during Bishop-Koop (patients 2-4) or Santulli jejunostomy (patient 1). The degree of hypoplasia in patients 1 to 4 was evaluated by counting the number of nerve cells with nuclear diameters greater than 8 μm in 3-μm slices in the entire circumference of the myenteric plexus. To simplify the numeration of nerve cells with standard H&E staining, only nerve cells with nuclear diameters greater than 8 μm were selected. These criteria were used previously to establish the reference range of neonatal controls [3].

We retrospectively analyzed the clinical course and nutritional status of these 4 patients using their case records.

3. Results

The number of ganglion cells in the biopsy taken from patients 2 to 4 was significantly reduced in both the jejunum (Fig. 1) and colon, and thick nerve strands in the sigmoid colon were absent. To definitively diagnose the degree of hypoganglionosis, further biopsies from whole circumferential sections of jejunum are required after 2 months (Table 1). This is because at least 2 months is required for sufficient cytological maturation before ganglion cells can be confidently recognized and counted in H&E-stained sections [3].

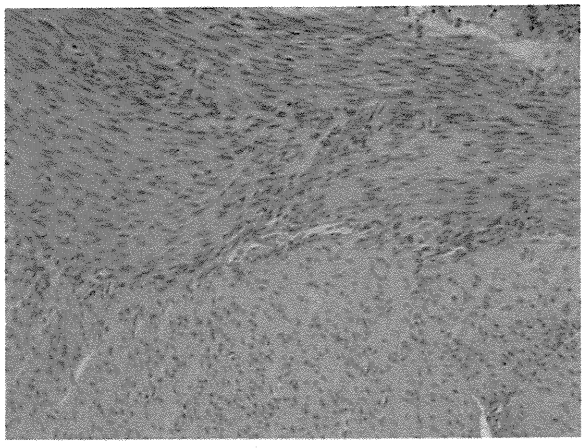

Fig. 1 Hematoxylin-eosin staining of the jejunum narrow plexus. Histological staining showed diminished numbers of ganglion cells in the narrow plexus from patient 1 at 2 years of age (×200).

An initial double-barrel jejunostomy less than 50 cm from the ligament of Treitz allowed patients 2 to 4 to commence oral nutrition within a week following surgery. Within the first month of age, transposition of the stoma at 85 cm from the ligament of Treitz to the oral site of 35 cm from the ligament of Treitz was performed in patient 1 because of persistent intestinal obstruction (Table 2).

Contrast studies were subsequently performed to confirm distal bowel motility. Following overnight confirmation of transit of the contrast medium to the colon by radiography, a thrice-daily infusion of 5 mL isotonic sodium chloride solution in addition to 0.3 g of lactobacillus and 0.3 g of GFO (Otsuka Pharmaceutical Factory, Inc, Tokyo, Japan) was commenced.

The initial double-barrel jejunostomy was subsequently refashioned to the Bishop-Koop type in patients 2 and 4 at 3 months of age. Patient 3 was delayed until 6 months of age owing to postponement of the scheduled surgery because the patient was recuperating from the common cold. The refashioning of stoma resulted in overall improvements in the nutritional and physical status of the patients (Fig. 2A, B). In patient 1, this refashioning was abandoned because of atrophic changes in the distal intestinal segment. Patients 2 to 4 only required intravenous hyperalimentation to fulfill less than half of their daily nutritional requirements (Table 3). They were able to successfully maintain their body weight within 1.5 SD of the normal mean body weight. Recent liver function test results also revealed normal liver transaminases and total bilirubin levels, except for patient 1 (Table 3). The patients were followed up multiple times over a period of 1 to 4 years.

4. Discussion

Excessively long segment congenital hypoganglionosis remains a diagnostic challenge [6], and the evaluation of its

Table 1 Number of nerve cells in the entire circumference of the myenteric plexus in 3-μm slices with standard H&E staining

Patient no.	Age at operation	Number of ganglion cells	Disease	Site of intestine for histological evaluation	Resected at
1[a]	2 y	34	Hypoganglionosis	Jejunum	Santulli op
2	3 m	19	Hypoganglionosis	Jejunum	Bishop-Koop op
3	6 m	14	Hypoganglionosis	Jejunum	Bishop-Koop op
4	3 m	33	Hypoganglionosis	Jejunum	Bishop-Koop op
Control 1	6 m	82	Internal hernia	Jejunum	Op for strangulated jejunum
Control 2	1 y	83	Cloacal anomaly	Ileum	Intestinal interposition vaginoplasty
Control 3	1 y	111	Cloacal anomaly	Ileum	Intestinal interposition vaginoplasty
Control 4	4 m	133	Jejunal stenosis	Jejunum	Op for jejunal stenosis

Op indicates operation.
[a] Initially treated in another hospital.

effects on intestinal function is difficult during the initial surgery. Toyosaka et al [7] reported on 12 cases of hypoganglionosis. All of these cases were initially diagnosed as extensive or total colonic aganglionosis. It was reported that neonatal enteric nerve cells are small in hypoganglionosis and hence may be misdiagnosed as aganglionosis. Furthermore, biopsies that sample only a small circumferential portion may not accurately estimate myenteric ganglion cell density, even when numerous sections are counted [8]. Therefore, the diagnosis may be suspected based on initial partial circumferential biopsies, but should be confirmed with a second whole circumferential section of the jejunum. Using a short segmental resection for diagnosis purposes may introduce unacceptable risks, particularly as the clinical relevance of mild to moderate change in the ganglion cell number has not been clearly defined. Therefore, we confirmed the initial diagnosis using interval full-circumference biopsy when the initial double-barrel jejunostomy was subsequently refashioned to the Bishop-Koop type.

Hypoganglionosis is also often misdiagnosed as aganglionosis in rectal suction biopsies when assayed using acetylcholinesterase enzyme histochemical techniques [6]. Thus, confirmation of hypertrophic nerve strands from sigmoid colon biopsies may be useful in distinguishing hypoganglionosis from aganglionosis, as the hypertrophic nerve strands that are found in patients with extensive or total colonic aganglionosis are absent in the sigmoid colon in hypoganglionosis [9]. However, hypertrophic nerves may be restricted to the distal rectum in some cases and the rectum in many cases in total colonic aganglionosis [10]. Pathologists rely on the absence of submucosal and myenteric ganglion cells to establish the diagnosis of Hirschsprung disease (HD) [11,12]. In contrast, hypoganglionosis primarily affects myenteric ganglion cells; and the density and distribution of submucosal ganglion cells in hypoganglionosis are relatively normal [9]. Following an adequately large biopsy of the sigmoid colon, the jejunum was favored for the biopsy, rather than the ileum in hypoganglionosis. In this study, all patients showed hypoplastic ganglia in both the colon and the jejunum, which may reduce the time taken for the surgery. Aside from the histological findings, the clinical appearance of the neonatal ileus is also an important diagnostic factor. As changes in the nuclei of ganglion cells occur over time [3], it is desirable to conduct biopsies at separate time intervals to make a definitive diagnosis of the disorder and conduct a comparison among the cases of hypoganglionosis. An increase in the nuclear diameter of ganglion cells occurs as part of the maturation process, also manifesting with improved intestinal motility [3].

Table 2 Initial stoma site and refashioned stoma site

Patient no.	Age	Sex	Type of stoma (age)	Initial stoma site from ligament of Treitz	Transposed stoma site from ligament of Treitz (age)
1[a]	3 y	F	DB (14th day)	85 cm	35 cm DB (1st month)
2	4 y	F	DB (5th day)	35 cm	NC
3	2 y	M	DB (1st day)	50 cm	NC
4	1 y	M	DB (8th day)	50 cm	NC

DB indicates double barrel; NC, no change.
[a] Initially treated in another hospital.

Okamoto et al [5] concluded that site selection for a stoma is a critical factor in the treatment of hypoganglionosis. In their report, the conventional treatment of HD was administered in 11 out of 25 patients, which also included 6 short form hypoganglionosis patients. Only 8 patients could be maintained on oral nutrition (including 6 that had short form hypoganglionosis); 2 patients were maintained on tube enteral nutrition, and 11 patients required total parenteral nutrition. The 5 patients were reported to have died in the course of the investigation. Ikeda et al [13] also reported on a failure-to-thrive case treated in the same manner that necessitated recreation of the jejunostomy.

Patients with excessively long segment congenital hypoganglionosis typically present with small bowel obstruction in the neonatal period. Because a change in the diameter of

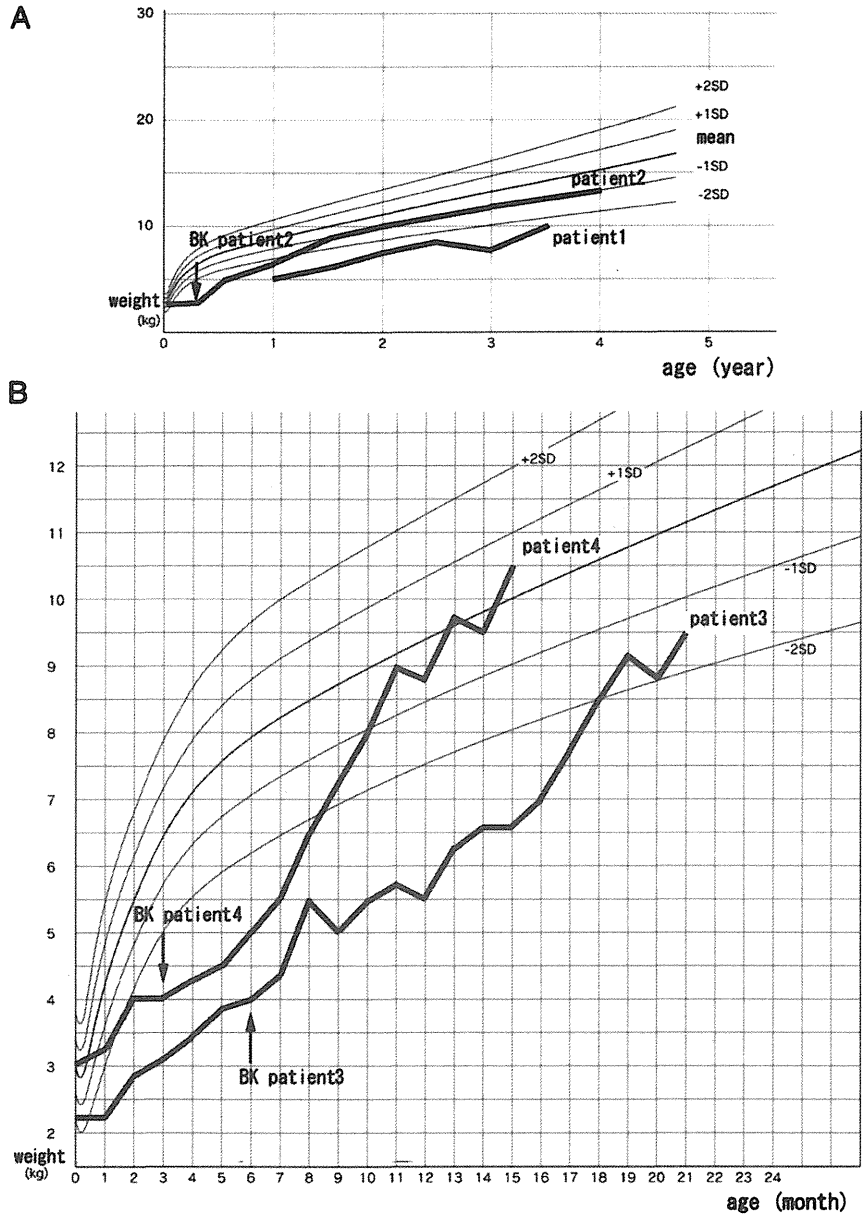

Fig. 2 Weight-age curve of each patient compared with a cross-sectional growth chart in 2000. A, Patient 1 and patient 2 (with the cross-sectional growth chart for 0- to 6-year-old Japanese girls). B, Patient 3 and patient 4 (with the cross-sectional growth chart for 0- to 2-year-old Japanese boys). The Bishop-Koop operation of patient 3 was postponed because of the patient's common cold and scheduling of the surgery. During this period, the patient's weight gain remained constant even with lactobacillus administration and GFO infusions. BK indicates Bishop-Koop operation; SD, standard deviation; arrow, timing of BK operation of each patient.

the distal small intestine predominates in many cases, an ileostomy is usually performed during the initial surgery. Unlike in Hirschsprung disease (HD), gut dysmotility usually persists following an ileostomy, necessitating the recreation of an ostomy in a more proximal intestinal segment [3,4,13]. Okamoto et al [5] previously reported that 13 patient required more than 3 times the number of intestinal surgeries including 4 patients that needed more than 5 times the number of intestinal surgeries being able to stabilize their intestinal condition. These multiple surgeries involve delayed enteral feeding and unnecessarily invasive treatments. Patients 2 to 4, in whom stomas were located less than 50 cm distal to the ligament of Treitz, could commence enteral feeding within a week following their upper jejunostomy.

Intestinal failure–associated liver disease is a significant complication arising from the management of hypoganglionosis and contributes to long-term morbidity and mortality in