Tomoaki Taguchi
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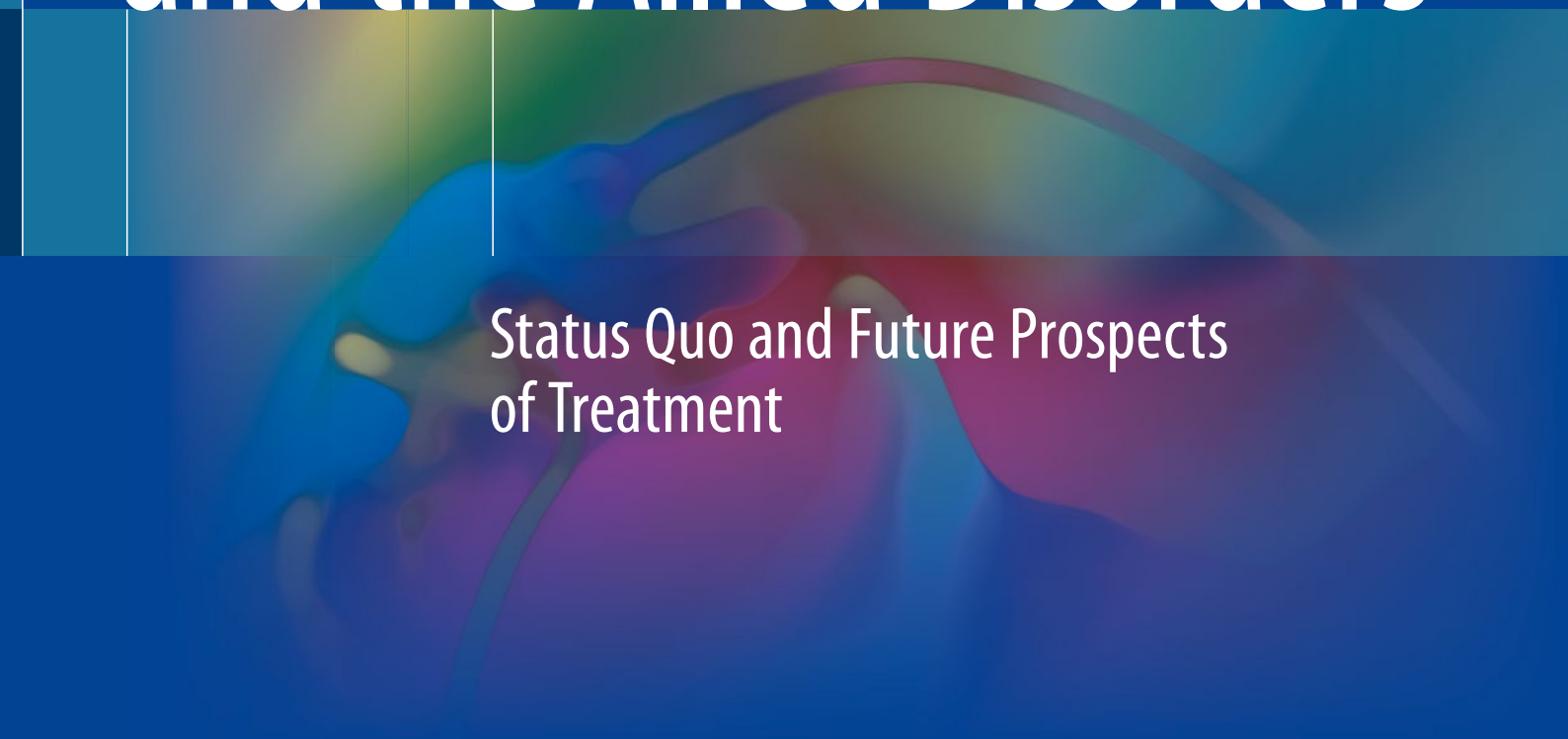
Editors

Hirschsprung's Disease and the Allied Disorders

Status Quo and Future Prospects of Treatment



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Preface

Japanese pediatric surgeons have been contributing and leading to the progress of the diagnosis and treatment of Hirschsprung's disease (HD) in the world. However, there has been no book in English concerning HD from Japan. Therefore, a few years ago, Mr. Takayama, Springer Japan, proposed us to edit and publish a book on HD in English. Just on time, we have established Japanese Study Group of HD and Allied Disorders of HD (ADHD) supported by a grant from the Ministry of Health and Labor and have collected data from a nationwide survey. Therefore, this has become an opportune time to edit and publish the international book about HD and ADHD from Japan.

HD is one of the surgically correctable diseases in children. Most of the pediatric surgeons, including those from Japan, have been interested in HD for a long time from the standpoint of the surgical procedure, the pathogenesis, the diagnostic tools, and the genetics. The cessation of craniocaudal migration of neural crest cells and the destruction of ganglion cells by ischemia or infection have been considered as the major pathogenesis. Namely, craniocaudal migration theory by Okamoto in 1967 and the presence of abnormally shaped arteries by Taguchi in 1985 were proposed from Japan. The presence of familial occurrence and the extent of aganglionic segment mainly restricted to the left colon are supported genetic influence. Currently, several candidates of responsible genes have been reported.

We have been performing a nationwide survey for 4 decades since 1978 to study the changing profile of HD in Japan. Nowadays, primary operations without laparotomy, including TAEPT and laparoscopy-assisted operations, have become the first choice for the definitive surgical treatment in Japan. The mortality rate has decreased over time and reached 2.4%. Most of the cases of death were patients with extensive aganglionosis.

ADHD have been understood as the conditions that clinically resemble HD, despite the presence of ganglion cells in the terminal rectum. The term "Pseudo HD" or "Variants of HD" has been sometimes used. We have performed a nationwide survey and collected ADHD cases for 10 years and demonstrated that those with congenital hypoganglionosis (HG), megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS), and chronic idiopathic pseudo-obstruction (CIIP) showed poor survival rate and poor quality of life. We have also completed the *Clinical Guidelines for ADHD*. This Guidelines will be published in English soon.

Finally, we are very happy to publish this book involving most of Japanese active pediatric surgeons, and also we would appreciate Mr. Takayama, Springer Japan, for his earnest passion and effort to design and publish this book.

Fukuoka, Japan — Tomoaki Taguchi
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Contents

Hirschsprung's Disease: A Historical Overview

1

Tatsuo Kuroda

Hirschsprung's disease is one of the most common and representative pediatric surgical diseases with the incidence of 1 out of 5000 live births. This disease is characterized by congenital megacolon and severe constipation, which sometimes result in fatal septic pathophysiology when remained untreated.

Development of the proper surgical procedure for Hirschsprung's disease is a successful example of application of the etiology and the pathophysiology of the disease clarified by basic researches, to the surgical clinics. The history of Hirschsprung's disease is overviewed in the present chapter with a focus on the initial description, the clarification of etiology, and the surgical innovation.

1.1 Description of Hirschsprung's Disease

The first known description of a pathological condition that is supposed to be Hirschsprung's disease appeared in an ancient Hindu literature, Sushruta Samhita, as an observatory note by an ancient Hindu surgeon Raveenthiran [1]. The first description of the disease in a modern scientific literature was an autopsy report of a 5-year-old girl by Frederick Ruysh in 1691 [2]. Thereafter, over 20 literatures regarding this pathological condition had been seen before Hirschsprung reported this disease according to a textbook. On the other hand, Mya first introduced the term "megacolon" in relation to this pathological condition in 1894 [3]. In 1886, Harald Hirschsprung, a pediatrician from Copenhagen, presented a report of two patients with an enlarged colon who died at 8 and 11 months of age, respectively, because of unrelenting constipation, malnutrition, and enterocolitis associated with fatal sepsis at the Pediatric Congress in Berlin [4]. Hirschsprung was the first to describe this pathological condition accompanied by a drastically enlarged colon as a distinct clinical entity. Since then, this specific condition has ultimately bore the name of Hirschsprung in order to honor his historical contribution on the disease. In 1908, Finney reviewed the disease and summarized the knowledge regarding this disorder to that date, which evoked the special interest with this unique disease to many researchers [5].

1.2 Clarification of Pathophysiology

Most of the patients with this congenital megacolon died because of malnutrition and septic enterocolitis at around the time when Hirschsprung first described the disease. However, the etiology of this congenital disorder had remained unknown for long. Since the introduction of the term "megacolon" by Mya [3], the enlarged colon had been paid more attention as the etiology of the disease. During the early 1900s, many theories and hypotheses were proposed regarding the etiology of Hirschsprung's disease. In 1901, Tittel [6] described the absence of intramural ganglion cells in the rectum of a 15-month-old infant who showed severe constipation since birth. Tittle's observation opened a way to clarify the etiology of this disease. Tittel's report was followed by many reports of the absence of intramural ganglion cells in the distal colon in the patients with this disease. Dalla Valle [7] also described the pathology and noted a familial occurrence of the disease in 1920 and 1924. In 1940, Tiffin et al. [8] also described the absence of ganglion cells in the distal colon in Hirschsprung's disease and suggested that the megacolon might be secondarily developed because of the passage failure due to the disturbance of intestinal peristalsis in the distal aganglionic intestine. This novel concept that neural imbalance in the distal non-dilated intestine caused its peristaltic malfunction and the secondary dilatation of the proximal intestines gradually gained stronger support by the researchers. Ehrenpreis [9] first paid surgical attention to the aganglionosis as the cause of congenital megacolon in 1946. He described a "dysfunction of evacuation" causing secondary dilatation of the proximal colon by barium enema studies and pointed out that Hirschsprung's disease could be

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diagnosed during the neonatal period. Zeulzer and Wilson in 1948 [10] and Robertson and Kernohan [11] in 1938 also correlated distal aganglionosis with the functional obstruction of the colon. Furthermore, Bodian et al. [12] also confirmed the convincing and unequivocal association of aganglionosis with Hirschsprung's disease. Thus, the etiology of Hirschsprung's disease was clarified and verified mainly during the first half of the last century.

1.3 Development of the First Successful Surgical Procedure

During the period when the dilated colon was still considered to be the primary lesion of Hirschsprung's disease and the true etiology and pathophysiology of the disease had not been clarified, the disease was almost universally fatal. The possible surgical treatment for Hirschsprung's disease was resection of the enlarged colon and creation of colostomy. The attempts of reanastomosis of the colon after resection of the enlarged colon were uniformly failed. The proximal intestines are supposed to dilate again like the preoperative state after reanastomosis, or anastomotic failure might occur postoperatively. Succeeding to the widespread recognition that the aganglionic intestines located beneath are responsible for this pathological condition, Swenson and Bill [13] first presented a curative surgical procedure for Hirschsprung's disease in 1948 based on this new concept of the disease. Orvar Swenson was born in Helsingborg, Sweden, in 1909 and migrated to Independence, Missouri, where he grew up in 1917. After having graduated from Harvard Medical School, he was a resident at the Peter Bent Brigham and the Boston Children's hospitals from 1938 to 1945. Then in 1945, Swenson became an assistant professor of Harvard Medical School in Boston. Alexander H. Bill was a pediatric surgeon at the Children's Orthopedic Hospital and the Department of Surgery, University of Washington, in Seattle. They were the first to resect the aganglionic colon and rectum and pulled through the proximal intestine with normal ganglion cells down to the anus. This procedure was now called Swenson's procedure. The procedure was originally performed without colostomy; however, the multistaged operation with creation of colostomy was also widely spread thereafter.

A new era of pediatric surgery was opened.

1.4 Improvement of the Surgical Procedure

The abdomino-anal pull-through procedure originally described by Swenson and Bill in 1948 was proved to show a satisfying clinical result over a long follow-up period. Swenson reported the results of 200 Swenson's procedures up to 10 years after operation early in 1957 [14]. The results for general health and bowel control were excellent with no frank incontinence. On the other hand, Rehbein and von Zimmermann reported in 1960 that some of their patients required repeated bougienage and follow-up barium enemas showed the dilatation of the colon again [15]. It was pointed out that the residual rectum after an unsuccessfully executed Swenson's procedure could produce residual symptoms. Furthermore, it was also pointed out that Swenson's procedure might endanger the pelvic nerves when not performed really properly and may arise some problems as for the urinary control and sexual function due to the injury of the pelvic neural plexus. High incidence of anastomotic leakage was also pointed out as the possible problem after this procedure. Novel procedures for Hirschsprung's disease were then developed during the 1950s and 1960s.

In 1956, Duhamel reported his retrorectal transanal pull-through procedure [16]. In Duhamel's procedure, the normoganglionic colon is brought down to the anus through the dorsal site of the aganglionic rectum where the nerve plexus is loose and anastomosed to the aganglionic rectum in a side-to-side manner. Thereafter, the posterior wall of the aganglionic rectum and the anterior wall of the pulled-through colon were resected to create a rectal pouch. This procedure was simple and had several advantages. Duhamel's procedure was associated with less risk for the damage of pelvic nerves and developed less anastomotic insufficiency. In addition, the preserved anterior rectum was expected to retain rectal sensation and avoid some of the postoperative problems. Later in 1959, Grob et al. [17] proposed a modification of Duhamel's procedure. He brought the colon into the rectum above the anal sphincter to avoid soiling. Duhamel then offered to bring the bowel down to the level about halfway up the internal anal sphincter. Ikeda [18, 19] proposed a further modification of Duhamel's procedure using a special forceps to remove the septum of the neorectum in 1966.

In 1964, Soave [20] reported the successful results of his novel procedure with a mucosal resection. Actually, this procedure was the adaptation of the similar techniques such as the procedure proposed by Ravitch and Sabiston [21] early in 1951 for familial polyposis and the other procedures proposed by Rehbein [22] in 1959 and by Romualdi [23] in 1960 for imperforate anus. Soave proposed to bring the normoganglionic colon down to the anal site through the rectal muscular cuff created by the resection of the mucosal layer. The pelvic nerve plexus is preserved, since the procedure involves only the luminal side of the rectum. In the original Soave's procedure, the pulled-through colon was not sutured primarily to the anal site and was remained unsutured until completion of auto-anastomosis. Denda and Katsumata [24] proposed a modified Soave's procedure, in which the normoganglionic colon was sutured primarily to the anal canal in 1966. Boley et al. [25] also reported the similar technique

later in 1968. This technique was called Soave-Denda-Boley procedure and became one of the most common definitive operations for Hirschsprung's disease along with the modified Duhamel's procedure.

The major surgical procedures now used for classical Hirschsprung's disease were thus all developed. The clinical outcome of these modified Soave's procedure and modified Duhamel's procedure is now considered to be basically similar as for the classical Hirschsprung's disease with the aganglionic segment extending not beyond the sigmoid colon. For the cases with longer aganglionic segment involving the total colon and more proximal intestines, Martin [26] proposed a surgical procedure similar to Duhamel's procedure, in which the proximal ganglionic intestine was anastomosed to the residual rectum in a long side-to-side style in 1968. However, the clinical outcomes for these cases with long aganglionic segment remain unsatisfying even in nowadays.

1.5 Innovation of the Diagnostic Technique

The increasing awareness of the importance of the early recognition of Hirschsprung's disease facilitated the development of not only the surgical procedures but also the diagnostic procedures for the disease.

The barium enema was required for the diagnosis of Hirschsprung's disease even in the earlier period. Neuhauser and his colleagues [27] reviewed the radiological images of the disease and demonstrated the narrow segment in the rectum and the distal colon, the transition zone, and the proximal dilatation corresponding to the aganglionic segment, the transitional segment, and the normoganglionic segment, respectively. Drastic change of the luminal caliber between the aganglionic and ganglionic segment in cologram characterized the disease and was known to be useful for the diagnosis.

Rectal biopsy was considered to confirm the diagnosis. A couple of different biopsy techniques were offered. In the earlier era, Bodian [28] proposed a relatively large biopsy of mucosa and submucosa, while Swenson, Fisher and MacMahon [29]; Bill et al. [30]; Hiatt [31]; and others proposed to take a deeper biopsy allowing examination of the intermuscular plexus in the 1950s. Back in 1953, Kamijyo et al. [32] reported the elevation of acetylcholine esterase activity in the aganglionic segment of Hirschsprung's disease. In 1972, Meier-Ruge [33] claimed clear differentiation of Hirschsprung's disease by the increased choline esterase staining of the mucosal layer, muscularis mucosae, and lamina propria with shallow specimens. They observed the increased acetylcholine esterase activity on the hyperplasic extrinsic nerve fibers and the giant nerve bundle in the aganglionic segment of Hirschsprung's disease that was stained by the Karnovsky-Roots method, an enzyme-histochemical method. This is the most specific and predictive finding to diagnose Hirschsprung's disease.

The absence of anorectal reflex observed in the anorectal manometry in Hirschsprung's disease was first reported by Callaghan and Nixon [34] in 1964, which was followed by the subsequent reports by Lawson and Nixon [35] in 1967 and by Schnaufer et al. [36] in 1967. In 1878, Gowers [37] described the observation that the internal anal sphincter relaxed with a rise in rectal tension in the normal patients. This phenomenon is now known as the recto-anal reflex. The absence of the reflex was applied in the diagnosis of Hirschsprung's disease and now became an essential examination for the disease. Several instruments for the anorectal manometry have been developed worldwide including our own.

Development and establishment of these diagnostic techniques enabled more accurate diagnosis of the disease in the younger period.

1.6 Recent Advance of the Research on Genetics and Embryonic Background

Many basic researches were conducted to clarify the embryological etiology of Hirschsprung's disease even during the later half of the last century. In 1967, Okamoto and Ueda [38] proposed the famous cranio-caudal migration theory based upon his histological observation using silver stain. He insisted that intestinal intramural ganglion cells migrate in the cranial-to-caudal direction during the early embryonic period and hypothesized that Hirschsprung's disease was evoked by the disturbance of this migration. Okamoto's work indicated the direction of subsequent researches on the embryology of Hirschsprung's disease.

In the 1990s, genetic background of Hirschsprung's disease was more precisely studied, and many gene mutations related to Hirschsprung's disease were reported. RET proto-oncogene encoding a tyrosine kinase receptor was the first gene reported in relation to Hirschsprung's disease [39]. Following after RET mutation in patients with Hirschsprung's disease, numerous observations of mutation of the genes including endothelin [40], endothelin receptor B [41], Sox-10 [42], Sip-1 (also known as ZFHX1-B) [43], Phox2B, and the Hedgehog/Notch complex [44] were reported in relation to the etiology of Hirschsprung's disease. These genes are playing roles in the migration and development of neural crest cells.

Furthermore, in the twenty-first century, several researches are in progress regarding the neural crest stem cell and regeneration of the intramural nerve plexus. At present, a novel therapeutic strategy for Hirschsprung's disease using the cell therapy has been proposed as a potential option [45].

1.7 Further Innovation of the Surgical Procedure

During the 1990s, laparoscopic surgery was introduced and widely spread in the pediatric surgical field. In 1994, Smith et al. [46] reported a case of Hirschsprung's disease successfully operated by the laparoscopic Duhamel's procedure. Then in 1995, Georgeson et al. [47] reported his initial experience of Soave's procedure performed laparoscopically in 12 cases. Subsequently, Hoffman et al. [48] in 1996 and Rothenberg and Chang [49] in 1997 also reported the successful completion of the laparoscopic Soave's procedure in infants and children. The laparoscopic procedures were established as the definitive surgery for Hirschsprung's disease. Some other novel techniques were also reported regarding the laparoscopic procedures. In 1998, Morikawa et al. [50] reported the prolapsing technique for laparoscopic Soave's procedure, in which the severed distal rectum was prolapsed and pulled out through the anus for mucosal resection.

Another major innovation in the definitive surgery for Hirschsprung's disease was made in the 1990s. Transanal mucosal resection instead of the conventional transabdominal technique in Soave's procedure was described by Saltzman et al. [51] in 1996. Thereafter, De la Torre-Mondragon and Ortega-Salgado [52] first described the totally transanal endorectal pull-through procedure in 1998. They reported the curative surgery for five patients with Hirschsprung's disease including a 24-day-old neonate without laparotomy or laparoscopic procedures. Technical innovation of surgery for Hirschsprung's disease still continues.

1.8 Future Tasks

Even though the clinical outcomes for the classical Hirschsprung's disease have been stabilized, treatment strategy for the patients with extremely long aganglionosis has not been established. Some of the clinical entities showing intestinal peristaltic disorder similar to Hirschsprung's disease have been known as variant Hirschsprung's diseases. The management and treatment for these pathological conditions remain unestablished.

Intestinal transplantation may be an important option for Hirschsprung's disease with extremely long aganglionic segment and variant Hirschsprung's disease. However, the clinical outcome of intestinal transplantation remains unsatisfying mainly because of difficulty in immunosuppression.

As an alternative treatment, some of the basic researches on the cell therapy using the intestinal stem cells have been reported. Future researches should be also directed for regenerative medicine of intestinal nerve plexus. Clinics and researches on Hirschsprung's disease are considered to be one of the most classical and, at the same time, the most advanced fields in pediatric surgery.

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Hirschsprung's Disease: Pathogenesis and Overview

2

Hisayoshi Kawahara

2.1 Historical Aspect

Hirschsprung's disease (HD) is a developmental disorder of the enteric nervous system (ENS) and is characterized by the absence of ganglion cells in the myenteric and submucosal plexuses of the distal intestine [1]. This results in absent peristalsis in the affected bowel and the development of a functional intestinal obstruction.

In 1887, Hirschsprung [2], a pathologist at Queen Louise Children's Hospital in Copenhagen, described two cases of the condition that ultimately bore his name. Although the clinical condition became well recognized, the pathologic features of HD were not understood, and multiple theories were entertained. The absence of ganglion cells in the distal colon of a child with HD was first noted by Tittel in 1901 [3]. In 1926, Fraser stated "This is an obscure disease of the large intestine, in which the essential features are an inability of the colon to part with its contents. The only curative treatment which the pathology and clinical course of the affection show to be applicable is that of excision of the affected bowel with the union of unaffected gut above to the upper end of the rectum below" [4]. Between this initial observation and the 1940s, several articles were published that documented abnormalities of innervation within the colon and recognized the absence of ganglion cells. The observation that the proximal colon was dilated and hypertrophied due to distal obstruction was noted by Ehrenpreis in 1946 [5]. Whitehouse and Kernohan [6] summarized the literature and presented a series of cases of their own that documented that the aganglionosis within the distal colon or rectum was the cause of the functional obstruction. In 1949, Swenson and colleagues [7] published an article recommending rectosigmoidectomy with preservation of the sphincters as the optimal treatment of this disease. Although surgical options, including various pull-through techniques, have been a consensus therapy and performed in clinical practice for years, the pathogeneses of HD remain unclear.

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2.2 Etiology

2.2.1 Migration of Neural Crest Cells

2.2.1.1 Cranio-caudal Migration

The neural crest is one of the earliest organs to form within the developing embryo. The neural crest cells (NCCs) are pluripotential and follow migratory pathways that are dependent on their axial level of origin. Once at their final destination, neuroblasts differentiate into numerous cell types. These include cells of the adrenal medulla, neurons and glia of the sympathetic and parasympathetic nervous systems, melanocytes, and neuroendocrine cells. Therefore, the diseases affecting the neural crest are diverse and have multiple manifestations. In 1974, Bolande [8] coined the term "neurocristopathy" to describe a diverse class of pathologies that may arise from defects in the development of tissues containing cells commonly derived from the NCC lineage. In HD, enteric NCCs fail to complete their rostrocaudal migration along the length of the intestine, leaving variable lengths of distal gut without ganglion cells. The ganglion cells of the enteric nervous system originate from the neural crest. HD is a classic example of a neurocristopathy, a disease arising from abnormalities of NCCs. In the human fetus, neural crest-derived neuroblasts first appear in the developing esophagus at 5 weeks' gestation; they migrate in a cranio-caudal direction down to the anal canal, where they appear during the 12th week of gestation [9]. Ganglion cells and their support cells originate in the vagal neural crest and migrate from there into the embryonic intestine [10]. The vagal neural crest is also the source of thymic stromal cells, parathyroid glands, and cardiac ganglion cells. Ganglion cells migrate first into Auerbach's myenteric plexus and then across the circular muscle layer into Meissner's submucosal plexus [1]. The NCCs first form the myenteric plexus just outside the circular muscle layer. The mesenchymally derived longitudinal muscle layer is formed, sandwiching the myenteric plexus after it has been formed in the 12th week of gestation. In addition, after the cranio-caudal migration has ended, the submucous plexus is

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formed by the neuroblasts, which migrate from the myenteric plexus across the circular muscle layer and into the submucosa; this progresses in a cranio-caudal direction during the 12th to 16th week of gestation [11]. Studies in mice that develop congenital aganglionosis suggested that there is a delay or arrest in this migration, which results in the NCCs failing to reach the distal bowel [12]. According to this theory, the length of aganglionic distal bowel is dependent on the timing of the arrest in cranio-caudal migration of the ganglion cells. The earlier the arrest of migration, the longer the aganglionic segment is.

2.2.1.2 Sacral Nerve Compensation

The pathological characteristics of HD are the absence of ganglion cells in the myenteric and submucosal plexuses and the presence of hypertrophied nerve trunks in the distal colon. The abnormal nerve bundles consist of cholinergic nerve fibers and are extrinsic parasympathetic nerve fibers of sacral origin [13]. It was suggested that the enteric neurons followed a dual gradient of development from each end of the gut toward the middle, with vagal NCCs providing the main source of enteric neurons and sacral NCCs innervating the hindgut [14, 15]. Tam and Lister [14] showed using immunohistochemical localization of neuron-specific enolase that development of the ENS was most advanced in the pylorus, less so in the colon, and least so in the ileum. Their findings indicated the hypothesis of a dual gradient of neuronal development proceeding from both ends to the middle of the gut in midtrimester human fetuses. Gershon et al. [15] reported experiments using two cell tracers to label sacral NCCs before migration. One marker was an intercalating fluorescent dye; the other was a replication-deficient retrovirus (LZlO). When the tracers were injected into the avian sacral crest, labeled cells were found in the postumbilical gut and ganglion of Remak. When the tracers were injected into the vagal crest, labeled cells were seen in the gizzard and duodenum. However, sacral injections did not result in the appearance of labeled cells, except in the hindgut. When the sacral nerve crest was injected with LZIO in mice embryos, it was possible to distinguish labeled neurons as well as labeled glial cells in the postumbilical bowel. However, a dual origin of enteric neurons has been questioned by several studies on chick embryos as well as human embryos [16–18]. Allan and Newgreen [16] isolated bowel segments from embryos at various stages of development. They grew the segments in the chorioallantoic membrane and found that the enteric neurons appeared in a cranio-caudal sequence, demonstrating a vagal source. Meijers et al. [17] transected the bowel in ovo at an early stage, before the passage of NCCs had occurred, preventing cranio-caudal migration of vagal NCCs. They found that the hindgut remained aganglionic, showing that there was no colonization by sacral NCCs. Fujimoto et al. [18] studied NCC migration in the developing gut in the human embryo using antineurofilament protein antibody and found that enteric ganglia originated from a single vagal neural crest source. They found that the NCCs first appear in the esophagus at 4 weeks of gestation and then migrate down along the gut in a cranio-caudal direction. Burns and Douarin [19] showed using quail-chick chimeric grafting in conjunction with antibody labeling to identify graft-derived cells, neurons, and glia that vagal NCCs initially migrated within the submucosa, internal to the circular muscle layer, before migrating outward, adjacent to blood vessels, toward the myenteric plexus region, whereas sacral NCCs, which also formed the entire nerve of Remak, were primarily located in the presumptive myenteric plexus region and subsequently migrated inward toward the submucosal ganglia. They raised a question why sacral NCCs failed to compensate for the absence of vagal NCC in HD. A possible explanation they made was that, in mammals, unlike the chick, the sacral neural crest does not contribute a significant number of precursors to the ENS. A second possibility was that, in order to colonize the hindgut, sacral NCCs require an interaction with vagal neural crest-derived precursors or neurons or with factors produced by them. This was based on their findings that sacral NCCs were only present in significant numbers after vagal NCCs had already extensively colonized the hindgut. Kenny and Tam [20] have speculated that in mammals, the migration of sacral NCCs follows vagal neural crest colonization and these cells in isolation are insufficient to rescue the loss of ganglion cells in HD. Puri and Shinkai [11] also speculated that interaction between sacral and vagal enteric NCCs may be necessary for sacral NCC contribution to the ENS.

2.2.2 Microenvironment

HD is possibly due to failure of development of NCCs after migration rather than failure of migration alone. NCCs arrive at their destination, but then may fail to survive, proliferate, or differentiate due to abnormalities within their microenvironment. Extracellular matrix (ECM) proteins have been recognized as important microenvironmental factors of the neuronal processing pathway in the early embryonal stage. The ECM is a three-dimensional acellular structure composed of tissue-specific combinations of a large number of collagens, proteoglycans (e.g., decorin and versican), and glycoproteins (e.g., fibronectin, laminins, and tenascins). ECM proteins can influence cell behavior (i.e., migration, proliferation, survival, and/or differentiation) by interacting with either secreted ligands or transmembrane receptors [21]. An abnormal composition of the ECM was reported in human aganglionic gut. The importance of the ECM was firstly investigated by Kamagata and Donahoe [22], who examined the influence on differentiation of cholinergic

innervation by fibronectin, collagen IV, laminin, and heparan sulfate in rat gut in organ culture. They demonstrated fibronectin added to the medium enhanced the choline acetyltransferase activity and antibody to fibronectin inhibited acetylcholinesterase staining and choline acetyltransferase activity. Addition of anti-laminin, anti-collagen IV, or anti-heparan sulfate did not affect either acetylcholinesterase staining or choline acetyltransferase activity. They revealed that fibronectin may be an important factor in cholinergic differentiation of the enteric nervous system during the post-migration stage of development. Pomeranz et al. [23] demonstrated that laminin promoted the development of neurons and facilitated neurite extension. The 110-kDa laminin-binding protein was expressed on the surface of the immediate precursors of enteric neurons and glia. Fujimoto et al. [18] studied the distribution of ECM proteins and cell-matrix interactions in the migration pathway of NCCs in the gut in the early human embryo using a panel of anti-ECM protein antibodies such as fibronectin, laminin, collagen type IV, and hyaluronic acid. They found that fibronectin produced the migration pathway for NCCs and promoted their adhesion to the final destination. Similarly, hyaluronic acid appears prior to the arrival of NCCs, and their immunoreactivity decreases once the NCCs settled. Hyaluronic acid also works as a cell adhesion molecule. Laminin and collagen type IV were promoting axonal processing and differentiation of ganglia rather than the NCC migration. Fibronectin, laminin, and collagen type IV tend to proceed into the developing human gut from the proximal esophagus to the distal rectum as gestation advances. They concluded that the alteration of these matrices in an early embryonal stage might cause the arrest of migration of NCCs to their final destination, which, in turn, may be a significant factor in the pathogenesis of HD. Parikh et al. [24] investigated the distribution of laminin and collagen type IV in the bowel specimens of neonates/infants with HD using indirect immunohistochemistry. Uniform distribution of laminin and collagen type IV was observed in the basement membranes of all control specimens. Strong laminin immunofluorescence was observed in the basement membranes of the inner circular layer, with diminishing intensity of immunofluorescence in the basement membranes of the outer layers of muscularis externa in the aganglionic bowel. An abnormal immunofluorescent staining pattern similar to that of laminin was also observed with collagen type IV. These abnormalities are strikingly similar to those reported in the presumptive aganglionic terminal bowel of fetal ls/ls mice. Payette et al. [25] found that the aganglionic bowel in the fetal ls/ls mice was thickened, and there were increased amounts of laminin and collagen type IV in the basal laminae and mesenchymal extracellular space. Parikh et al. [26] reported that more intense immunofluorescence for both fibronectin and tenascin, relative to controls and proximal normoganglionic zones of HD, was observed in the basement membranes of the smooth muscle layers of the muscularis mucosae and muscularis externa in the aganglionic and transitional zones in the bowel of neonates/infants with HD. Alteration of ECM in the early embryonal stage may cause the arrest of migration of NCCs to their final destination, thus producing HD, or may result in abnormal development of enteric ganglia, thereby producing HD-related disorders (e.g., intestinal neuronal dysplasia). Recently, Zheng et al. [27] have investigated the expression of fibronectin and the correlated abundance of neuroligins in the ENS. They found that both neuroligin-1 and neuroligin-2 were expressed at low levels in aganglionic segments and at intermediate levels in transitional segments compared to their high level of expression in normal tissue. In contrast, fibronectin expression was negatively correlated with expression in these three samples transitioning from highest to lowest. They concluded that fibronectin affected the expression of both neuroligin-1 and neuroligin-2 in HD, which might lead to the hypoplasia of ganglion cells in the ENS. However, it has not been clarified yet whether the ECM alterations represent the cause of aganglionosis or whether they are secondary changes.

Langer et al. [28] investigated if smooth muscle cells from the aganglionic region could affect neuronal development in vitro by adding neurons from neonatal mouse superior cervical ganglia to cultures of smooth muscle obtained from normal or aganglionic regions of patients with HD. Progressive increase in the diameter of the nerve cell body was consistently inhibited by 15–22% in neurons grown on aganglionic muscle compared with normal controls over the 6-day test period. It was implied that smooth muscle of the aganglionic colon was less favorable for neuronal development than the normally innervated region, and this might reflect an abnormality of cellular interaction causing HD.

2.2.3 Cell Adhesion Molecules

Cell adhesion molecules play an important role in cell-cell interactions, which regulate the development and maintenance of multicellular organisms. In the nervous system, there are unique cell adhesion molecules that are essential for elaborate neural network formation [29]. A range of cell surface molecules has been studied and shown to contribute to cell-to-cell recognition processes in normal adult and developing tissues. One of the best characterized is neural cell adhesion molecule (NCAM). NCAM is a cell surface glycoprotein involved in adhesion between several types of neural cells and their processes and in the formation of initial contact between nerve and muscle cells. NCAM has been detected on central and autonomic neurons and skeletal and cardiac myofibers and has been suggested to play an important role in the

development and maintenance of the neuromuscular system. Romanska et al. [30] demonstrated there was a marked increase in NCAM expression in the muscle, particularly in the muscularis mucosae and characteristic hypertrophied nerve bundles of the intermuscular zone and submucosa displayed immunoreactivity for NCAM in aganglionic bowel. NCAM immunoreactivity was seen in ganglion cells and nerve fibers throughout the gut wall and, more weakly, on the inner border of the circular muscle in normal colon. In mature tissue, the expression of NCAM is reduced substantially and is restricted to the neuromuscular junction. Re-expression of NCAM occurs after experimental denervation and in response to injury of muscle and/or nerve. They suggested that increased NCAM expression in the aganglionic bowel reflected the immaturity of differentiation of both nerves and muscle, with the resulting impaired peristaltic activity. In contrast, Kobayashi et al. [31] studied expression of NADPH-diaphorase and NCAM in the colon from patients with HD using immunohistochemical techniques. They showed a selective absence of NADPH-diaphorase- and NCAM-positive nerve fibers in the circular as well as longitudinal muscle of aganglionic bowel, whereas these immunoreactive nerve fibers were present in abundance in the muscle of ganglionic colon of patients with HD as well as in the colon of controls. It was indicated that the lack of expression of NCAM on nerve fibers within the muscle of patients with HD suggested a developmental abnormality of innervation of the muscle, and the selective absence of NADPH-diaphorase-positive nerves in the muscle was most likely responsible for the spasticity of the aganglionic segment.

Ikawa et al. [32] conducted immunohistochemical studies to examine the expression of three neural membrane proteins, Thy-l and neural cell adhesion molecule L1 (L1CAM), which belong to the immunoglobulin superfamily, and integrin α5, a receptor protein of fibronectin, in the ganglionic and aganglionic segment in patients with HD. LICAM is a multidomain protein and plays important roles in cell adhesion, migration, neurite outgrowth, fasciculation of axons, and myelination. They found that hypertrophied nerve bundles observed in intermuscular space, in submucosa, and in circular muscle layer were immunopositive with anti-Thy-l and anti-integrin α5 antibodies, but not immunostained with anti-L1. It was implied based on their finding that the lack of L1CAM expression in extrinsic nerve fibers can perturb NCC migration and adequate neurite outgrowth with resulting aganglionic segment and abnormal nerve bundles of extrinsic fibers in the colon of patients with HD. Recently, several cases of X-linked hydrocephalus (XLH) accompanied by HD have been reported. A Japanese boy with XLH-HD showed the L1CAM gene with a C61T mutation in exon 1, resulting in a truncating nonsense mutation at amino acid position 21 and producing an extremely short protein that was unlikely to interact with other proteins [33].

2.2.4 Neurotrophic Factors

Nerve growth factor (NGF) is the best-characterized neurotrophic molecule and is known to be an essential factor for the development and the functional maintenance of selected neurons such as the peripheral sensory and sympathetic neurons. This molecule is target-derived and is required specifically by sympathetic and dorsal root ganglion cells for their survival and maturation during embryonic and early postnatal development. A physiological role of NGF in the central nervous system is known as a neurotrophic factor for the cholinergic neurons in the basal forebrain, whereas it remains unclarified whether NGF plays an important role in the normal development of the ENS. Kuroda et al. [34] studied NGF expression both at the protein and mRNA level in normal and aganglionic intestines of piebald-strain mice and also in human specimens. They found that NGF production is altered in the aganglionic intestines and also in the "transitional zone" in HD, suggesting that abnormal NGF function might be a potential etiologic factor of aganglionosis.

Glial cell line-derived neurotrophic factor (GDNF), a distant member of the transforming growth factor-β superfamily, was originally identified as a potent neurotrophic factor secreted from a rat glial cell line that promotes the survival of midbrain dopaminergic neurons. Subsequently, it was shown to act as a potent survival factor for motor neurons as well as numerous populations of peripheral nervous system neurons, including enteric ganglia. GDNF is the first identified ligand of *RET*, which is a major gene causing HD. Sánchez et al. [35] reported that GDNF-null mice displayed renal agenesis, severe pyloric stenosis, and dilatation of the proximal intestine and were detected with no ENS neuron in the stomach and intestine at birth, suggesting that, although some ENS neurons could develop in the absence of GDNF, they died during late embryonic development. Martucciello et al. [36] firstly examined GDNF expression in infants with HD, showing cholinergic hyperinnervation and hypertrophic trunks of nerve fibers in the muscular interstitium with complete absence of GDNF expression and a reduced GDNF immunoreactivity in the small ganglia of the hypoganglionic segment. Ohshiro and Puri [37] reported that the number of GDNF-immunoreactive epithelial cells in the mucosa of aganglionic bowel was significantly lower compared with the normoganglionic bowel and that the level of GDNF peptide was significantly lower in the aganglionic bowel on ELISA analysis. Kusafuka and Puri [38] reported that the signal for *RET* mRNA expression was significantly less intense in the aganglionic bowel than in the normoganglionic bowel in patients with HD. The finding of a reduced level of GDNF in the aganglionic bowel as well as a reduced number of GDNF-immunoreactive cells in the mucosa of aganglionic bowel, together with the observation of decreased *RET* mRNA expression in the aganglionic bowel, suggested that GDNF may play a role in the pathogenesis of

HD [29]. Iwashita et al. [39] reported using rat experimental models that genes associated with HD were highly upregulated in enteric NCCs relative to whole-fetus RNA, and one of these genes, GDNF receptor *RET*, was necessary for NCC migration in the gut. They concluded that GDNF promoted the migration of NCCs in culture, but did not affect their survival or proliferation, and HD might be caused by defects in neural crest stem cell function.

NEDD4-like ubiquitin protein ligase 2 (NEDL2) plays an important role in many physiological and pathological processes. NEDL2 is a positive regulator of GDNF/*RET* signaling, which plays a crucial role during the proliferation, migration, and differentiation of NCCs. O'Donnell et al. [40] showed that NEDL2-immunoreactivity colocalized with interstitial cells of Cajal and neurons within the submucosa, myenteric plexus, and smooth muscle in controls and ganglionic specimens, with markedly reduced NEDL2 immunoreactivity in the aganglionic specimens. The decreased expression of NEDL2 in the aganglionic colon may suggest that NEDL2 may play a role in the pathophysiology of HD.

Neurotrophin-3 (NT-3) and its high-affinity receptor, tropomyosin receptor kinase C (trk C), are important in the enteric neuronal development. Facer et al. [41] reported using blinded quantitative immunohistochemical analysis that the proportion of submucous plexus trk C-immunoreactive neurons was reduced in the colon from patients with HD and idiopathic slow-transit constipation, and decreased trk C expression might reflect developmental abnormalities in HD.

2.2.5 Immunologic Response

Major histocompatibility complex (MHC) class II antigen is a cell surface glycoprotein involved in the immune recognition of foreign tissue and in the regulation of the immune response. In order to induce an immune reaction, antigen must first be processed intracellularly and then be presented on the cell surface as peptides bound to the MHC molecules expressed on the antigen-presenting cells. The antigen-MHC complex is then recognized by the T-cell receptor on the T-lymphocyte membrane. Activated T cells mediate an array of immunologic effector mechanisms that can lead to tissue damage. MHC molecules, especially class II, are known to play a major role in pathological states. Hirobe et al. [42] demonstrated using colonic biopsy specimens of HD patients that there was marked elevation of MHC class II expression in the aganglionic areas, especially within the hypertrophied nerve fibers, and the ectopic presence of MHC class II expression in and about the neural elements of HD could be considered aberrant and abnormal. They suggested that ectopic expression of class II antigen might indicate that an underlying immunologic mechanism is responsible for HD. Intercellular adhesion molecule-l (ICAM-l) is pivotal in many inflammatory and immune paracrine interactions, playing a major role in the process of leukocyte adhesion and regulation of leukocyte extravasation and infiltration into inflammatory tissues. Kobayashi et al. [43] studied expression of intercellular adhesion molecule-1 (ICAM-1) and major histocompatibility complex (MHC) class II antigen in patients with HD using indirect immunohistochemistry. There was strong expression of ICAM-1 and MHC class II antigen on hypertrophic nerve trunks, in both the submucous and myenteric plexuses of the aganglionic colon. The transition zone showed strong expression of ICAM-1 and MHC class II antigen on small ganglia in the myenteric and submucous plexuses. However, no staining of ganglia or nerve fibers was found in the submucous and myenteric plexuses of the colon from controls or in the ganglionic colon from patients with HD. The expression of both antigens on hypertrophic nerve trunks suggested the presence of an immunologic response in the pathogenesis of HD.

Moore et al. [44] reported that IgG and IgM were significantly increased in segments of bowel histologically identified as aganglionic or transitional zone. They suggested that increased IgM in the neonatal period indicated an early immune response in HD and strengthened the hypothesis that the immune system might be involved in its pathogenesis.

2.2.6 Epithelial-Derived Signal

Sonic hedgehog (Shh) secreted from epithelium is important in a number of morphogenetic events during gut development. Shh expression is first detected in the endodermal epithelium just after the establishment of the digestive tube and continues throughout development. During early development of the mouse, Shh is required both for maintenance of the epithelium and for its own expression in endoderm. Later in development Shh is involved in the region-specific differentiation of both the epithelium and mesenchyme. Sukegawa et al. [45] reported that endoderm-derived Shh is responsible for the patterning across the radial axis of the gut through induction of inner components and inhibition of outer components, such as smooth muscle and enteric neurons. Fu et al. [46] showed with cell and organ culture that Shh promoted proliferation but inhibited neuronal differentiation of enteric NCCs and restricted GDNF-induced NCC migration. They considered that Shh possibly regulated the development of neural plexuses by modulation of the responsiveness of NCCs toward GDNF inductions and/or regulation of the proliferation and differentiation of NCCs in gut. Nagy et al. [47] found that Shh overexpression, achieved in ovo using Shh-encoding retrovirus and in organ culture using recombinant protein, led to intestinal aganglionosis, and Shh inhibited enteric NCC proliferation, promoted neuronal

differentiation, and reduced expression of GDNF, a key regulator of ENS formation. They suspected that the gradient of epithelial-derived Shh protein in the lamina propria led to the creation of an inhibitory ECM environment that prevented enteric NCCs from migrating too close to the epithelium, counteracting the chemoattractive effect of netrin [48] and thus contributing to patterning the submucosal plexus.

2.2.7 Autophagy

One of the hypotheses of HD is that the absence of ganglion cells in the distal part of the gut is caused by the death of enteric NCCs following migration. Huang et al. [49] showed typical autophagosome structures found in the Auerbach plexus of both the narrow and transitional segments. Real-time PCR results showed that Beclin1 mRNA and LC3 mRNA were the highest in the narrow segment, whereas p75 was the highest in the dilated segment. Immunohistochemistry analyses indicated a consistent result with mRNA levels, by increased Beclin1-positive and LC3-positive neurons but reduced p75-positive neurons in the Auerbach plexus of the transitional segment compared with the dilated segment. Their findings indicated that autophagy existed in the bowel of patients with HD. On the basis of the detection of the highest expression of the autophagy genes in the narrow segment, autophagy might additionally cause the lack of neurons. Ge et al. [50] reported with real-time PCR that apoptosis-inducing factor and calpain-1 mRNAs were highly expressed in the transitional segment, whereas autophagy protein 5 (Atg5) was highly expressed in the narrow segment. Correlation analysis indicated an inverse correlation between calpain-1 and Atg5 mRNA levels in both the narrow and transitional segments. They concluded that apoptosis occurred in the aganglionic bowel based on their results.

2.2.8 Genetics

HD is one of the best understood human complex genetic diseases. Several observations indicating the genetic origin of HD are as follows [51].

1. Average risk of recurrence in siblings of 3–4%, about 200-fold higher than in the normal population.
2. Increased prevalence in males.
3. Association with other genetic diseases and chromosomal abnormalities.
4. Presence of genetic models of aganglionosis with a specific mode of inheritance.

The high proportion of sporadic cases, approximately 80%, variable lengths of aganglionosis among relatives, and incomplete penetrance, i.e., some mutation carriers do not have aganglionosis, support a multigenic model to explain the predominantly non-Mendelian inheritance pattern of non-syndromic cases [51]. As might be predicted by the complex cellular mechanisms needed to form the ENS, proliferation, migration, and controlled differentiation, many gene defects can increase HD risk. Linkage analyses in large HD families led to the identification of the *RET* gene (10q11.2) as the first gene shown to be involved in HD. Gabriel et al. [52] clarified that noncoding mutations in *RET* were important with 3p21 and 19q12 as modifiers of *RET* expression in short-segment HD and that their frequency was probably higher in short-segment than in long-segment HD. Hofstra et al. [53] reported with the survey of 95 patients with HD that *RET* mutations were found in 9 out of 17 familial cases (53%), all containing long-segment HD, and in 11 of 78 sporadic cases (14%), none having long-segment HD. Emison et al. [54] reported that a common noncoding *RET* variant within a conserved enhancer-like sequence in intron 1 is significantly associated with HD susceptibility and makes a 20-fold greater contribution to risk than rare alleles do. In contrast, Griseri et al. [55] identified a "protective" *RET* haplotype, which was underrepresented in HD patients with respect to controls, and demonstrated that the protective effect of this haplotype was due to a variant located in the 3′ untranslated region of the *RET* gene, which slowed down the physiological mRNA decay of the gene transcripts. In addition to *RET*, mutations have been identified in over a dozen other genes, but these account for a minority of cases [56]. While *RET* mutations are the major risk factor in this disease, evidence suggests that they may not be sufficient on their own to result in aganglionosis [56]. The majority of cases appear to be multigenic, comprising a combination of *RET* mutations with genetic abnormalities at other loci, with these interactions impacting the incidence and severity of the aganglionosis. Carrasquillo et al. [57] reported statistically significant joint transmission of *RET* and *EDNRB* alleles in HD patients and concluded that genetic interaction between mutations in *RET* and *EDNRB* was an underlying mechanism for HD. Cantrell et al. [58] tested for association between genes in the endothelin signaling pathway (*EDNRB*, *EDN3*, *ECE1*) and severity of aganglionosis in an extended pedigree of *B6C3FeLe. Sox10* Dom mice. Their data demonstrated that *SOX10-EDNRB* interactions could influence the development of the ENS in mouse models and suggested that this interaction could contribute to the epistatic network producing variation between patients with HD. An important role has also been described for modifier genes. These are genes that, when mutated, do not result in a phenotype, but, when present with a mutation in another gene, they worsen the effect [51]. A simplified list of genes that impact ENS development is shown in Table 2.1 [59]. The details of HD genetics are described in Chap. 3 (genetic aspect).

Table 2.1 Genes that impact ENS development [59]

Gene	Role in ENS development	Protein function/comments
RET	Supports ENS precursor survival, proliferation, migration, neuronal differentiation, neurite growth, and axon patterning	Transmembrane tyrosine kinase receptor Most commonly inactivated gene in people with HD
GDNF	*RET*-activating ligand	Neurotrophic factor Rarely mutated in people with HD
EDNRB	Prevents premature differentiation of NCC Facilitates colon colonization by NCC	G-protein-coupled receptor Mutated in 5% of people with HD Mutation causes hearing loss and pigmentation defects (Waardenburg-Shah)
EDN3	*EDNRB*-activating ligand	Peptide Rarely mutated in people with HD
SOX10	Required for bowel colonization by NCC Activates *RET* expression	Transcription factor Mutations cause HD plus hearing loss and pigmentation defects (Waardenburg-Shah)
PHOX2B	Required for bowel colonization by NCC Activates *RET* expression	Transcription factor Mutations cause HD plus congenital central hypoventilation (Haddad syndrome)

ENS enteric nervous system, *NCC* neural crest cell, *HD* Hirschsprung's disease.

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3 Genetic Aspect of Hirschsprung's Disease

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3.1 Hirschsprung's Disease

Hirschsprung's disease (HSCR) is a congenital disorder pathologically characterized by an absence of enteric ganglion cells along a variable length of the distal gut [1]. It is a developmental disorder that is caused by a failure of enteric neural crest-derived cells (ENCCs) to colonize the entire gut [2–4]. The ENCCs form the enteric nervous system (ENS) and originate mainly from vagal neural crest cells that invade the foregut and migrate in a rostral to caudal direction to colonize the entire foregut, midgut, caecum and hindgut [5]. Sacral neural crest cells also make a contribution in mice and chicks, but a much smaller one, to colonize the colon [6, 7]. In HSCR, the absence of ENCCs leads to tonic contraction of the affected segment and intestinal obstruction. This obstruction may lead to failure to pass the first stool within 48 h after birth, vomiting and massive distension of the proximal bowel (also called megacolon) or neonatal enterocolitis [2, 4].

3.2 Epidemiology and Classification

The incidence of HSCR is estimated at 1/5000 live births [8, 9]. However, the incidence varies significantly among ethnic groups (1.0, 1.5, 2.1 and 2.8 per 10,000 live births in Hispanics, Caucasian-Americans, African-Americans and Asians, respectively) [4, 10]. HSCR is classified into two types, according to the extent of aganglionosis [11]. Short-segment HSCR (S-HSCR) occurs most commonly (80%) and affects the rectum and a short portion of the colon, whereas long-segment HSCR (L-HSCR) affects longer tracts of the colon [12, 13]. Rare cases present as total colonic aganglionosis (TCA) or total intestinal aganglionosis (TIA) [8, 11]. There is a sex bias with a preponderance of affected males and a sex ratio of 4 [8]. Interestingly, the male-female ratio is significantly higher for S-HSCR (4.2–4.4) than for L-HSCR (1.2–1.9) [8, 10].

The majority of patients with HSCR are sporadic S-HSCR cases; however, HSCR can also be inherited. Generally, familial forms of HSCR have incomplete penetrance and show variability in the extent of aganglionosis, and their transmission is influenced by gender (male > female) [4, 11]. In Table 3.1, we summarize the epidemiology and male-biased recurrence risk in HSCR.

Although HSCR occurs as an isolated trait in most cases (70%) [4], it can also occur as part of a number of syndromes consisting of various other congenital abnormalities in 18% of the cases [2, 4]. In the latter group of patients, some monogenic syndromes can be recognized [2, 4]. Finally, HSCR is also associated with chromosomal abnormalities, which accounts for up to 12% of HSCR cases [2, 4]. The most common chromosome abnormality associated with HSCR is Down's syndrome (trisomy 21), which occurs in 2–10% of all individuals with HSCR [14]. Conversely, approximately 0.6–3% of individuals with Down's syndrome have HSCR [15].

Table 3.1 Epidemiology and recurrence risk figures in HSCR

	L-HSCR	S-HSCR
% probands	19	81
Sex ratio (male/female)	1.75	5.5
Genetic model	Dominant	Multifactorial
Penetrance (%) (male/female)	52:40	17:4
Recurrence risk to sibs[a] (%)		
Male probands	17/13	5/1
Female probands	33/9	5/3

Relative risk = 200

[a]Recurrence risk is given for male/female siblings, respectively

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Table 3.2 Genes associated with non-syndromic HSCR (partially involved in syndromic HSCR)

Gene	Location	OMIM	Phenotype	Inheritance	Frequency
RET	10q11.2	164761	Non-syndromic HSCR/MEN2A	Dominant, incomplete penetrance	50% familial, 15–35% sporadic
GDNF	5p13.1	600837	Non-syndromic HSCR	Non-Mendelian	Rare sporadic cases
NRTN	19p13	602018	Non-syndromic HSCR	Non-Mendelian	Rare sporadic cases
EDNRB	13q22	131244	Waardenburg-Shah syndrome	Recessive	
			Non-syndromic HSCR	Dominant, de novo 80%	3–7%
EDN3	20q13	131242	Waardenburg-Shah syndrome	Recessive	
			Non-syndromic HSCR	Dominant, incomplete penetrance	~5%
ECE1	1p36	600423	HSCR, cardiac and autonomic nervous system dysfunction	De novo dominant	Rare sporadic cases
NRG1	8p12	142445	Non-syndromic HSCR	Dominant, unknown penetrance	<1%
NRG3	10q23.1	605533	Non-syndromic HSCR	Dominant, unknown penetrance	<1%
SEMA3C	7q21.11	602645	Non-syndromic HSCR	Dominant, unknown penetrance	<5%
SEMA3D	7q21.11	609907	Non-syndromic HSCR	Dominant, unknown penetrance	<5%

3.3 Explorations in Genetics of HSCR

The familial HSCR within the human population allows human geneticists to use a range of approaches to identify susceptibility loci [11]. At the same time, genetic studies in model organisms such as mice and zebrafish are identifying genes that lead to HSCR-like phenotypes. The identification of mice with HSCR-like phenotypes has prompted human geneticists to look for mutations at the corresponding loci in their patient samples [2, 3]. Furthermore, identification of new HSCR loci in humans has generated interest in creating new genetic models in mice or zebrafish to help better understand the pathogenesis of HSCR [3]. In Table 3.2, we describe the collective output of these studies and summarize currently identified HSCR-associated genes.

3.4 The RET and the Endothelin Signalling Pathway

Among various HSCR-associated genes, *RET* (rearranged during transfection) and *EDNRB* (endothelin receptor type B) are the most important.

Heterozygous mutations in the *RET* receptor tyrosine kinase account for 15–35% of patients with sporadic HSCR and 50% of familial cases [2, 4, 11], whereas noncoding mutations in *RET* are suggested to impart susceptibility in other HSCR cases [11, 16, 17]. Deletion of *Ret* in mice leads to complete intestinal aganglionosis [18]. Activation of the RET receptor occurs upon dimerization through the formation of a complex between ligands and co-receptors, such as glial cell line-derived neurotrophic factor (GDNF), and its glycosylphosphatidylinositol (GPI)-anchored co-receptor GDNF family receptor α1 (GFRα1). The essential function of this ligand/receptor complex in normal ENS development is underscored by the fact that equivalent aganglionosis phenotypes are observed in mice and zebrafish in the absence of *Ret*, *Gdnf* or *Gfrα1* [18–22]. Moreover, patients with HSCR have been identified who carry heterozygous mutations in *GDNF* [23].

Ret and *Gfrα1* are expressed in ENCCs upon entry into the gut, whereas *Gdnf* is expressed in the gut mesoderm [2–4]. In vitro studies show that GDNF is a chemoattractive signal for ENCCs and have suggested that GDNF attracts migrating *Ret*- and *Gfrα1*-expressing ENCCs to their proper target region in the developing gut [24, 25].

The other GDNF family ligands, neurturin (NRTN), artemin and persephin, can bind and activate RET via their respective GPI-anchored co-receptors GFRα2, GFRα3 and GFRα4. Of these proteins, NRTN and GFRα2 have been implicated in ENS development as mice lacking Nrtn or GFRα2 exhibit ENS defects, such as decreased gut motility associated with reduced density of projections from excitatory cholinergic neurons [26, 27]. Consistent with this finding, in rare cases patients with HSCR have been identified carrying mutations in *NRTN* [28].

A second signalling pathway that is known to have a key role in ENS development is mediated by the endothelin-3 (EDN3) ligand and its G-protein-coupled receptor EDNRB. Patients with HSCR have been identified who carry heterozygous mutations in *EDN3*, *EDNRB* and endothelin-converting enzyme *ECE1* (which converts an inactive precursor form of EDN3 into an active form), and these patients comprise approximately 5% of human HSCR cases [2, 4]. Homozygous mutations in *EDNRB* and *EDN3* are associated with Waardenburg syndrome, which is characterized by colonic aganglionosis, pigmentation defects and deafness [2, 4, 11]. In addition, mice carrying loss of function mutations in *Edn3*, *Ednrb* or *Ece1* exhibit aganglionosis and pigmentation defects [29–31]. *Ednrb* is expressed primarily by migrating ENCCs, whereas *Edn3* is expressed in the midgut and

hindgut mesoderm [32, 33]. Like GDNF-GFRα1-RET signalling, EDN3-EDNRB signalling is implicated in ENS development, as well as in coordinating normal colonization of the gut by ENCCs.

3.5 Interaction Between Pathways

How the multiple pathways involved in normal ENS development coordinate their functions is the subject of much current study. Genome-wide association studies (GWAS) have revealed associations between the inheritance of *EDNRB* mutations and certain *RET* alleles in patients with HSCR (although no *RET* mutations were identified) [34]. This joint transmission of *EDNRB* and *RET* alleles in patients with HSCR suggests a genetic relationship between these two loci. This idea is supported by genetic studies in the mouse. Mice homozygous for the recessive hypomorphic allele of *Ednrb* (*Ednrb*^{s}, which only rarely exhibit aganglionosis) and heterozygous for a *Ret* null mutation (*Ret*$^{+/-}$, which do not exhibit aganglionosis) show high frequencies of aganglionosis [34, 35]. Similar genetic studies show that, whereas *Ret*$^{51/51}$ and *Edn3*$^{ls/ls}$ mice display colonic aganglionosis, combinations of these mutant alleles lead to almost complete intestinal aganglionosis [32]. Together, these studies suggest that genetic interactions occur between GDNF-GFRα1-RET and EDN3-EDNRB signalling pathways. Further studies show that EDN3 and GDNF have synergistic effects on the proliferation of ENS progenitors [32].

3.6 Other Genes Related to Non-syndromic HSCR

GWAS has identified two paralog genes in the same gene family, *NRG1* and *NRG3* as HSCR-associated genes. Rare coding pathogenic variants in *NRG1* have been identified [36], whereas benign *NRG1* variants in conjunction with *RET* variants also infer increased susceptibility to HSCR, especially in the Chinese population [37]. NRG1 encodes a growth factor that is expressed in intestinal mucosa. Most cases have been associated with short-segment, non-syndromic disease [36, 37]. Copy-number variants (mostly deletions) in NRG3 (a paralog of NRG1) have also been implicated in HSCR pathogenesis [38, 39].

More recently, pathogenic variants have been described in two genes within four class 3 semaphorins, *SEMA3C* and *SEMA3D*, and are enriched in those with HSCR over controls [40]. Benign variants in the semaphorin 3 cluster of genes have also been implicated as conferring increased susceptibility to development of HSCR, especially in conjunction with RET benign variants [40]. These proteins are involved in neuronal migration, proliferation, survival and/or axonal guidance. Variants in *SEMA3C* and *SEMA3D* predicted to be deleterious had a combined frequency of 4.7% in one survey of individuals with short-segment HSCR [40].

3.7 Multigenic Inheritance of Isolated HSCR

As mentioned above, *RET* plays a key role in HSCR genesis, and multiple genes may be required to modulate clinical expression. On the other hand, genetic heterogeneity where mutation in one of several genes is sufficient for phenotypic expression of HSCR has been demonstrated (*RET, EDNRB, EDN3, ECE1* and so on). Segregation studies in HSCR showed that the recurrence risk in siblings varies from 1.5% to 33% depending on the gender and the length of the aganglionic segment in the proband and the gender of the sibling (Table 3.1) [8, 41]. Consequently, HSCR has been assumed to be a sex-modified multifactorial disorder, the effect of genes playing a major role as compared to environmental factors (relative risk of 200). According to the segregation analysis where an autosomal dominant model in L-HSCR and a multifactorial model in S-HSCR were more likely, different approaches should be chosen to test these hypotheses in L-HSCR and S-HSCR independently.

3.8 The Unanswered Question of Male Sex Bias of HSCR

The 4:1 male sex bias of HSCR is currently poorly understood at the molecular level. It has been previously proposed that an X-linked gene may be responsible for the HSCR sex bias. In this regard, it is noteworthy that a small subset of patients suffering from hydrocephalus associated with mutations of the X-linked gene *L1CAM* also display HSCR [42]. However, the estimated incidence of HSCR among patients with mutations in the *L1CAM* gene is low (around 3%), and no mutation in *L1CAM* or any other X-linked gene has been identified through genome-wide association studies thus far [4, 43].

Epigenetic effects at the *RET* locus have also been hypothesized. Of note, a sex difference in disease expressivity (i.e. length of the aganglionic segment) in single- and double-mutant mice of short-segment aganglionosis involving hypomorphic *Ret* and *Ednrb* alleles has been observed [35].

3.9 Syndromic HSCR

Associated congenital anomalies are found in 18% of the HSCR patients. The one occurring at a frequency above that expected by chance includes gastrointestinal malformation, cleft palate, polydactyly, cardiac septal defects and

Table 3.3 Monogenic syndromic forms of HSCR

Syndrome	Features	Inheritance	Chromosome locus/ gene	% with HSCR
Bardet-Biedl syndrome	Dystrophy, obesity, ID, polydactyly, hypogenitalism, renal abnormalities	AR	At least 14 loci/ genes	2–10%
Cartilage-hair hypoplasia-anauxetic dysplasia spectrum disorders	Short-limbed dwarfism, sparse hair, immune defects	AR	9p13.3/*RMRP*	7–9%
Congenital central hypoventilation syndrome (CCHS)	Hypoxia, reduced ventilatory drive, neuroblastoma	AR	4p13/*PHOX2B*	20%
Goldberg-Shprintzen syndrome	Craniofacial, microcephaly, ID, PMG	AR	10q22.1/*KIF1BP*	Common
L1 syndrome	ID, hydrocephalus, ACC, adducted thumbs	XLR	Xq28/*L1CAM*	Rare
MEN 2A/FMTC	MTC, pheo, hyperparathyroidism	AD	10q11.21/*RET*	<1%
MEN 2B	MTC, pheo, mucosal and intestinal neuromas, skeletal abnormalities, corneal changes	AD	10q11.21/*RET*	Rare
Mowat-Wilson syndrome	ID, microcephaly, craniofacial, CHD, ACC, epilepsy, short stature	AD	2q22.3/*ZFHX1B*	41–71%
Waardenburg syndrome type 4 (Waardenburg-Shah syndrome)	Pigmentary abnormalities, deafness	AR (usually)	13q22.3/*EDNRB* 20q13.32/*EDN3*	Common
		AD	22q13.1/*SOX10*	Almost 100%

ID intellectual disability, *CHD* congenital heart disease, *PMG* polymicrogyria, *AD* autosomal dominant; *AR* autosomal recessive, *XLR* X-linked recessive, *pheo* pheochromocytoma, *MTC* medullary thyroid carcinoma, *ACC* agenesis of the corpus callosum. (1) Limited data are available. (2) In FMTC, affected individuals do not have pheochromocytoma or hyperparathyroidism

craniofacial anomalies [44, 45]. The higher rate of associated anomalies in familial cases than in isolated cases (39% vs 21%) strongly suggests syndromes with Mendelian inheritance [45]. Assessment of all HSCR patients by a trained dysmorphologist should provide a careful evaluation for recognizable syndromes.

Haploinsufficiency for *SOX10*, an SRY-related high-mobility group (HMG)-box transcription factor, is associated with HSCR in Waardenburg syndrome [4, 11]. Similar phenotypes affecting neural crest-derived cell lineages (ENS and melanocytes) are also observed in mice and zebrafish lacking *Sox10*, which exhibit total intestinal aganglionosis and hypopigmentation [46–48]. SOX10 is expressed in vagal neural crest cells as they emigrate from the neural tube and is a marker of ENS progenitors [2, 3, 49]. In the absence of *Sox10*, mice possess a smaller pool of ENS progenitors, strongly indicating a role for SOX10 in maintaining progenitor states [50, 51]. At later stages of ENS development, SOX10 is expressed in the glial cell lineage and is proposed to function in cell fate specification and glial cell differentiation [52].

Mutations in the transcription factors paired-like homeobox 2b (*PHOX2B*) and zinc finger homeobox 1b (*ZFHX1B*, also known as *SIP1*) have been identified in patients with HSCR in congenital central hypoventilation syndrome (CCHS) and Mowat-Wilson syndrome, respectively [53, 54]. *Phox2b* is expressed in migrating ENCCs, and mice and zebrafish that lack *Phox2b* display aganglionosis [55, 56]. *Zfhx1b* is expressed in the premigratory and migratory neural crest cells, and mice lacking *Zfhx1b* show a complete absence of vagal neural crest precursors [57]. Mutations in *KIF1BP* have also been identified in patients with HSCR in Goldberg-Shprintzen megacolon syndrome [58]. The molecular function of KIF1BP is unknown, and no corresponding mouse mutations exist. Finally, syndromes frequently associated with HSCR are listed in Table 3.3.

A large number of chromosomal anomalies have also been described in HSCR patients. Down's syndrome (trisomy 21) is by far the most frequent, involving 2–10% of ascertained HSCR cases [10–12]. In these cases, both the unbalanced sex ratio (5.5–10.5:1) and the predominance of S-HSCR are even greater than in isolated HSCR. Overexpression of gene(s) on chromosome 21 and predisposing to HSCR has been hypothesized and a susceptibility gene mapping to 21q22 postulated in a Mennonite kindred [59]. However, these data were not confirmed [60]. Coding sequence mutations in genes predisposing to HSCR, *RET*, *EDNRB* and *GDNF* were found in a small number of patients with Down's syndrome and HSCR [61, 62]. However, the common HSCR predisposing *RET* hypomorphic allele is over represented in patients with Down's syndrome and HSCR when compared to patients without HSCR [63].

3.10 Genetic Counselling

HSCR is a sex-modified multifactorial congenital malformation with an overall recurrence risk in sibs of the proband of 4% (relative risk = 200). In isolated HSCR, adequate relative risk will be provided by taking into account the sex and length of the aganglionic segment in the proband and the gender of the sibling (2–33%). The highest recurrence risk is

for a male sibling of a female proband with L-HSCR (Table 3.1). According to poor genotype-phenotype correlation thus far, the benefit of mutation screening for HSCR patients appears low except for systematic testing of the *RET* gene. This, however, is still not routine practice in most countries. Many HSCR cases are associated with other congenital anomalies. In these cases, the long-term prognosis is highly dependent on the severity of the associated anomalies. Several known syndromes have straight Mendelian inheritance. This emphasizes the importance of careful assessment by a clinician trained in syndromology of all newborns diagnosed with HSCR.

3.11 Recent Progress and Future Directions

Although a number of genes have been implicated in HSCR, mutations in these genes account for just over half of familial HSCR cases and a smaller proportion of sporadic cases.

Regarding HSCR-associated gene discovery, analyses using whole-genome sequencing (WGS) or whole-exome sequencing (WES) of DNA from HSCR patients are currently underway. Recently, several novel genes (*DENND3*, *NCLN*, *NUP98* and *TBATA*) have been identified as HSCR-associated genes through WES coupled with unbiased in vivo functional analysis with genetically modified zebrafish [64]. Furthermore, WES coupled with in vitro functional analysis using patient-derived induced pluripotent stem cells (iPSCs) has revealed novel HSCR-associated gene mutation in *VCL* [65]. Notably, mutation correction in iPSCs via CRSPR/Cas9-mediated genome editing restored iPSC-derived ENCC function, demonstrating strong evidence for validating genotype-phenotype correlation of HSCR with patient-derived cells.

Additional comprehensive genetic screen with a robust functional analysis will provide us new insights into human multigenic disorders including HSCR.

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4 Craniocaudal Migration/ Neurocristopathy

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4.1 Craniocaudal Migration Theory

In 1967, Okamoto and Ueda [1] reported using 18 human embryos and fetuses in the gestational age ranging from 5 weeks to 9 months that the myenteric plexus was formed by neuroblasts which were distributed to the alimentary tract by craniocaudal migration during the fifth to the twelfth week of gestation. This historical concept of the craniocaudal migratory formation of intramural plexus in human is as follows.

At the fifth week of gestation, a pair of strong vagal nerve trunks already reached the upper esophagus. The rectum received a few fine nerve fibers from the pelvic and preaortic plexuses located behind the rectum. The sympathetic ganglionated chains were formed bilaterally ventral to the vertebral column throughout its entire length, but no intramural ganglia were yet present in any portion of the alimentary tract at this stage. A group of immature ganglion cells, neuroblasts, was found bilaterally along the vagal trunks at the level of the pharynx. At the sixth week, neuroblasts appeared around and along the esophagus, just outside the circular muscle layer in close relation to the pre-existing vagal nerves. These neuroblasts were followed on serial sections down to the cardia of the stomach, but no neuroblasts were found in the remaining part of the gastrointestinal tract below the corpus of the stomach. At the seventh week, neuroblasts were seen in the esophagus, stomach, duodenum, and most of the cephalic limb of the midgut, but not as yet in the caudal limb of the midgut and the rectum. Only a considerable number of fibers were found in the distal part of the caudal limb and rectum. At this stage, prevertebral sympathetic ganglia developed, and a few fine nerve fibers were traced from them to the intestinal wall via the mesentery. At the eighth week, neuroblasts were in most of the intestine except for the distal half of the colon and the rectum. Neuroblasts were seen in a surprisingly high density in the entire esophagus of the fetus, contrary to the findings in the adult's esophagus containing fewer ganglion cells in its upper 2/3 than in any other part of the alimentary tract. This suggested a distribution of gradient neuroblasts along the alimentary tract in a craniocaudal fashion. At the twelfth week, neuroblasts were eventually found in all parts of the intestine down to the end of the rectum. Some neuroblasts were found at the base of the urinary bladder at this stage, though it was not certain whether these neuroblasts were derived from the same source of neuroblasts supplying the intestine.

Neuroblasts which appeared in the alimentary tract wall first formed the myenteric plexus just outside the circular muscle layer. At the seventh week, the primary network of the myenteric plexus was observed in the stomach. The submucosal plexus was formed by the neuroblasts which migrated from the myenteric plexus across the circular muscle layer into the submucosa. The formation of the submucosal plexus progressed in a craniocaudal fashion during the period from the third to the fourth month. The process of the craniocaudal development of the myenteric plexus is illustrated schematically in Fig. 4.1. Based on these embryological findings, Okamoto and Ueda suggested that Hirschsprung's disease (HD) was a development anomaly, in which the developmental process of the intramural plexus had ceased at various stages before the twelfth week of gestation. The earlier the cessation, the longer the segment of aganglionosis. However, the question why migration ceased in a fetal life was left unanswered in their study.

4.2 Neural Crest Cell Migration

The enteric nervous system (ENS) originates from vagal and sacral neural crest populations that migrate to the fetal gut in the developing embryo [2]. In the mouse, vagal neural crest

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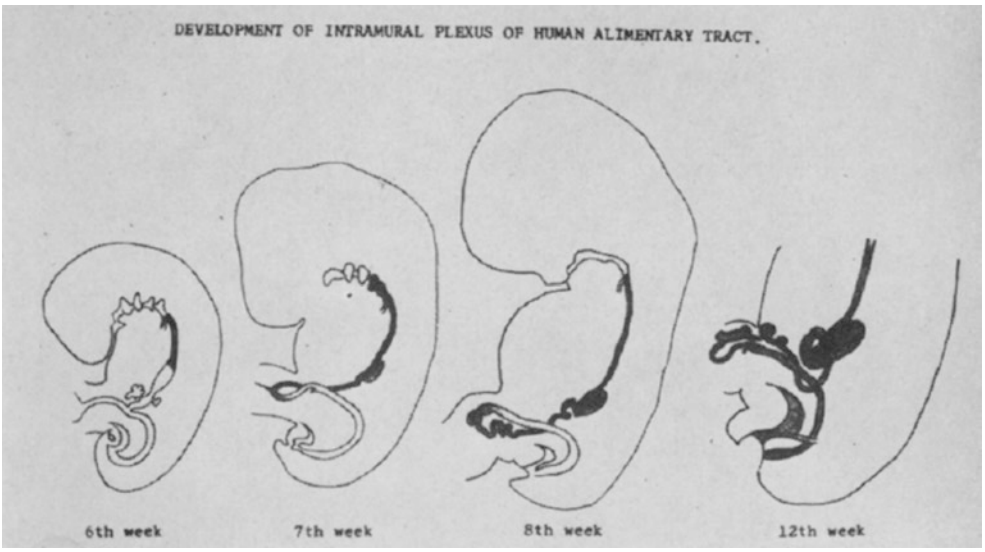

Fig. 4.1 Diagram showing development of the myenteric plexus in a human embryo. (Reproduced with permission from Okamoto and Ueda [1])

cells (NCCs) emigrate from the neural tube to the foregut and migrate caudally to populate the entire gut. Sacral NCCs delaminate later from the neural tube, enter the hindgut, and migrate rostrally, opposite the vagal NCCs, to co-populate the post-umbilical portion of the gut [3]. It has long been accepted that NCCs either enter the foregut mesenchyme proximally and migrate down its length in a rostral to caudal fashion (vagal NCCs) or they enter the gut at the distal end and migrate caudal to rostral (sacral NCCs). These processes left unexplained how subsets of HD patients exhibit "skip segment" aganglionosis. Skip segment HD (SSHD) involves a "skip area" of normally ganglionated intestine, surrounded proximally and distally by aganglionosis. O'Donnell and Puri [4] performed a systematic review of SSHD reported in the literature between 1954 and 2009. In their review, 24 cases of SSHD had been reported in the literature. Of the 24 SSHD cases, 18 (75%) were males, and 22(92%) were with total colonic aganglionosis (TCA), and 2/24 (8%) were rectosigmoid HD. Of the 22 TCA cases, 9 (41%) had a skip segment in the transverse colon, 6 (27%) in the ascending colon, and 2 (9%) in the cecum, and 5 (23%) had multiple skip segments. In both rectosigmoid SSHD cases, the skip segment was in the sigmoid colon. Overall, the length of the skip segment was variable, with the entire transverse colon ganglionated in some cases. How skip segment aganglionosis might arise remained unclarified, although it was suggested that extramural NCCs could account for the ganglionated skip segments seen in some SSHD cases. Recently, mechanistic data have emerged that can explain the role of transmesenteric NCCs in SSHD. Nishiyama et al. [5] have reported using time-lapse imaging analyses of mouse NCCs that a population of NCCs crossed from the midgut to the hindgut via the mesentery during a developmental time period in which these gut regions were transiently juxtaposed and that such transmesenteric NCCs constituted a large part of the hindgut ENS by taking a shortcut to the colon. This migratory process required GDNF signaling. They suggested that impaired transmesenteric migration of NCCs might underlie the pathogenesis of HD. Obermayr et al. [6] explained timetable and migratory pathway of NCCs along the embryonic mouse gut in their recent review (Fig. 4.2). NCCs enter the foregut around developmental stage E9 and migrate caudally within the gut mesenchyme (shown with green in Fig. 4.2). At E11.0–E11.5, there is a transient apposition of the midgut and postcecal gut, and a subpopulation of vagal NCCs (shown with purple in Fig. 4.2) takes a shortcut across the mesentery to colonize the colon. The transmesenteric cells give rise to the ENS in a large part of the colon. Vagal NCCs reach the anal end of the gut around E14.5. Cells derived from the sacral neural crest (shown with blue in Fig. 4.2) emigrate to the vicinity of the hindgut around E11.5 but then undergo a waiting period and enter the distal hindgut around E13.5 along with nerve fibers arising from extrinsic neurons. As the gestation period for a mouse is approximately 19 days, colonization of the gut by NCCs takes >25% of the gestation period. In humans, NCC migration takes about 3 weeks, beginning around week 4 and ending by week 7. Butler Tjaden and Trainor [7] emphasized on the limited time window, while NCCs destined for the hindgut traverse the mesentery as solitary cells. The midgut and hindgut are opposed in parallel only between E10.5 and E11.5, and the transmesenteric NCCs are the major source of the ENS in the hindgut. If transmesenteric NCCs delayed migration through the mesentery, the result should be impaired colonization of the hindgut. They also proposed the importance of a limited time window critical for complete ENS colonization of the terminal hindgut. A change in the microenvironment occurs at E14.5 when the gut is no longer permissive to migrating NCCs, and high laminin levels may play a role in this

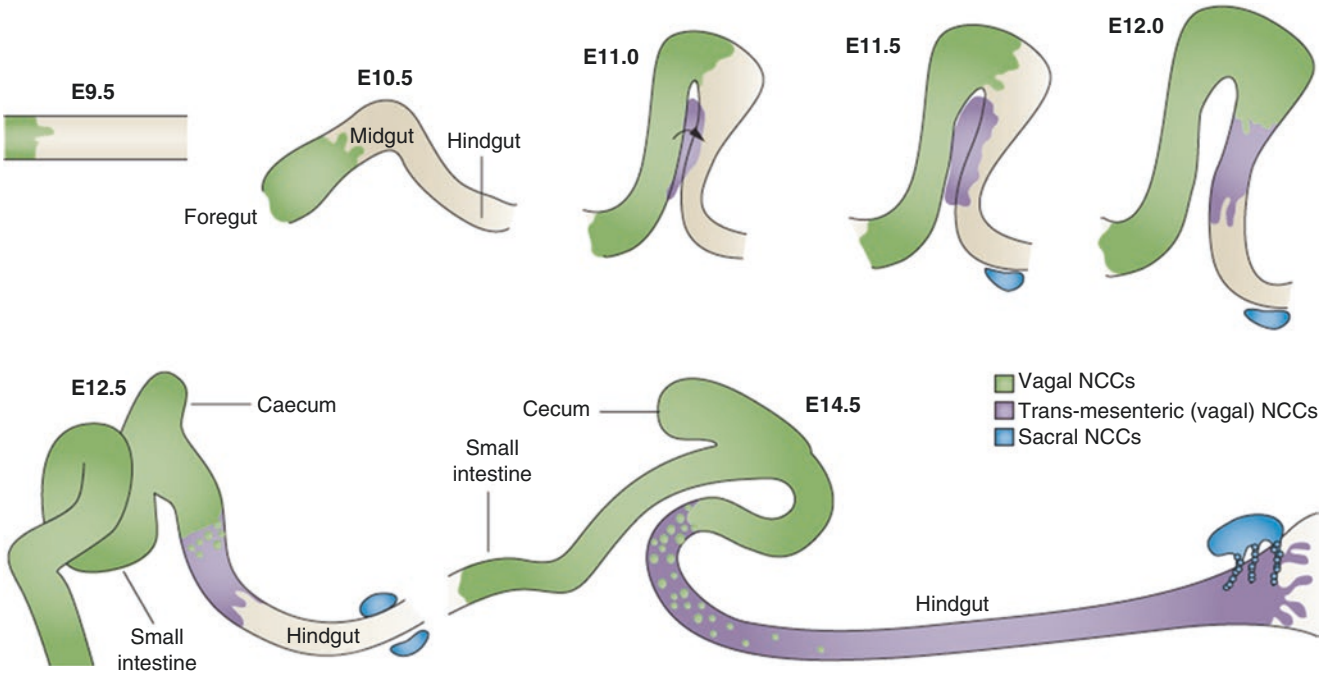

Fig. 4.2 Timetable and migratory pathway of NCCs along the embryonic mouse gut. *NCC* neural crest cell, *ENS* enteric nervous system. (Reproduced with permission from Obermayr et al. [6])

nonpermissive environment. Druckenbrod and Epstein [8] identified in mice changes in laminin expression at E14.5 that are associated with the failure of NCCs to invade the hindgut. Therefore, it could be assumed that delayed colonic arrival of NCCs is sufficient to cause HD due to environment changes in the colon. In contrast, Barlow et al. [9] reported continued and complete colonization of the entire colon throughout E14.5–E18.5, a period in which the gut is considered to be nonpermissive or less permissive to NCCs. Their findings may indicate that there is not a strict permissive time window of NCC colonization and delayed migration does not unequivocally equate with a predisposition for the pathogenesis of HD.

4.3 Neurocristopathy

4.3.1 Simple and Complex Neurocristopathy

In 1974, Bolande [10] proposed the term "neurocristopathy" for a category of diseases arising in neural crest development. Schematic representations of early neural crest development in his historical publication are shown in Fig. 4.3. He cited Horstadius's consideration regarding neural crest in the beginning: "The neural crest is a very peculiar structure. As it originates so early, it has been called one of the primary organs in the development of the vertebrate embryo. But is has only a temporary existence, as its cells are soon dispersed throughout the body, differentiating into many tissues" [11]. Bolande divided maldevelopment of NCCs into two basic forms: "simple neurocristopathy," which is characterized by a single pathologic process, generally unifocal and localized, and "complex neurocristopathies and neurocristopathic syndromes," which are multifocal and varied associations of simple neurocristopathies. In the original Bolande's classification, simple neurocristopathy included pheochromocytoma, neuroblastoma, medullary carcinoma of the thyroid, carcinoid tumors, HD, and melanotic progonoma, and complex neurocristopathies and neurocristopathic syndromes included von Recklinghausen's disease; Sipple's syndrome (pheochromocytoma and medullary thyroid carcinoma), multiple mucosal neuroma syndrome, multiple endocrine adenomatosis, neurocutaneous melanosis, and sundry associations and interrelated complexes [10]. In 1997, Bolande [12] reviewed the growth and development of the category of neurocristopathy during the past 20 years and newly defined neurocristopathies. Neurocristopathies consisted of two general types: dysgenetic and neoplastic. The dysgenetic neurocristopathies are essentially congenital malformations resulting from derangement of neural crest migration, colonization, or cytodifferentiation. The neoplastic neurocritopathies are true neoplasms, preneoplastic hyperplasias, or hamartomas. In either manifestation, a neurocristopathy may be singularly expressed in an organ or site in either the dysgenetic or neoplastic forms. These were termed simple neurocristopathies. They may also occur in multiple sites and

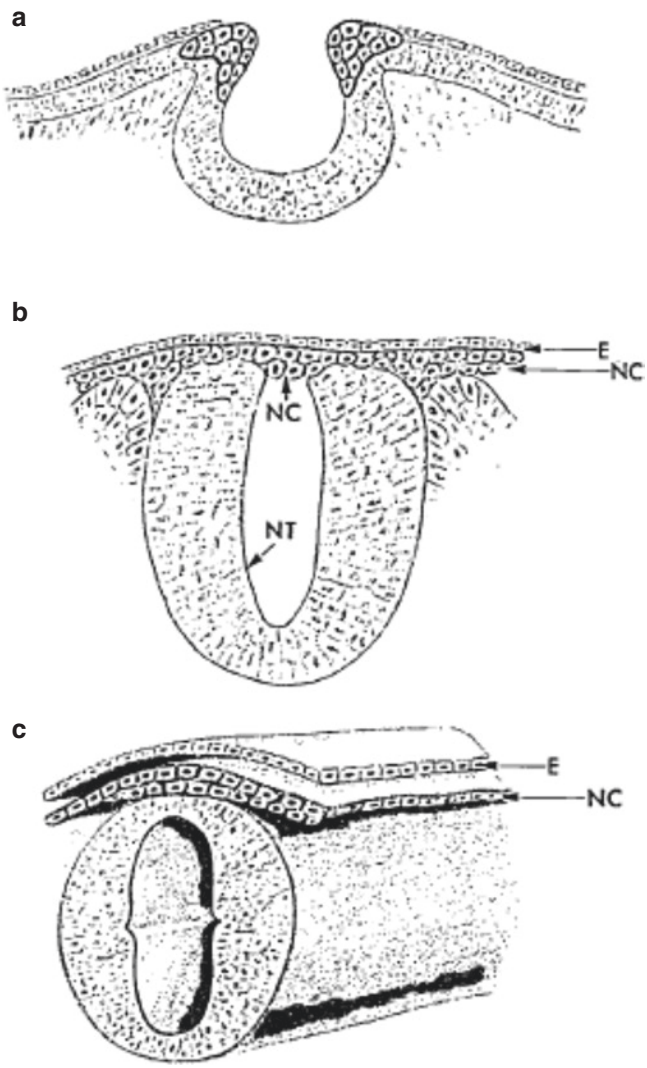

Fig. 4.3 Schematic representations of early neural crest development. (**a**) Early neurulation in a 2.5-week-old human embryo (cross section). Lateral parts of the neural plate ectoderm proliferate and become raised to form parallel neural folds. These form the margin of the neural groove. The darkly stippled areas are the anlagen of the neural crest. (**b**) Neurotubulation in a 3.5-week-old human embryo (cross section after Horstadius [11]). Dorsal coalescence of the fused neural folds forms the primitive neural tube. It is capped at its point of closure by the darkly colored neural crest anlagen (NC). Tile neural tube becomes separated from the dorsal layer of ectoderm (E) destined to become epidermis. The neural crest cell mass flattens out and begins to proliferate laterally. (**c**) Bilateral neural crest formation in a 4-week-old human embryo (after Arey). The neural crest tissue has formed two large parallel wedges extending from the dorsolateral aspects of the neural tube (NC). This tissue is now completely separated from the overlying ectoderm (E). Both the right and the left neural crest masses migrate ventrally and laterally through rapid proliferation of their constituent cells, migrating to many areas of the body. (Reproduced with permission from Bolande [10])

forms, sometimes combining dysgenetic and neoplastic forms. These were termed complex neurocristopathies. Bolande [12] presented a new list of the major neurocristopathies; some neoplasms were eliminated from the original list and others added (Table 4.1).

Table 4.1 The major neurocristopathies [9]

Simple neurocristopathies
A. Dysgenetic
Hyperpigmentary disorders: congenital melanocytic nevi, lentigo, ephelides, café au lait spots, neurocutaneous melanosis
Hypopigmentary disorders: albinism, partial albinism (piebaldism)
Hirschsprung's disease, intestinal neural dysplasia, or hyperganglionosis
Craniofacial malformations of cranial mesectodermal origin: Treacher Collins syndrome, frontonasal dysplasia, acrofacial dysostosis, Pierre Robin syndrome, facial clefting syndromes, anterior eye chamber anomalies, Goldenhar syndrome, fetal alcohol syndrome, isotretinoin embryopathy
B. Neoplastic
Neuroblastoma, C-cell carcinoma of the thyroid, pheochromocytoma, carotid body tumor, paragangliomas, melanotic progonoma, peripheral neuroectodermal tumors (PNETs) and Ewing's tumor, meningiomas
Complex neurocristopathies
A. Dysgenetic
Waardenburg's syndrome
Waardenburg's syndrome with Hirschsprung's disease
Piebaldism with Hirschsprung's disease
DiGeorge syndrome and variants
B. Neoplastic
Von Recklinghausen's disease
Multiple endocrine neoplasia (MEN) types 2A and 2B
C. Neoplastic and dysgenetic
Neuroblastoma with Hirschsprung's disease, DiGeorge syndrome, and von Recklinghausen's disease
Neuroblastoma with opsimyoclonia, heterochromia iridis, and Ondine curse
Familial neuroblastoma and Hirschsprung's disease
MEN2 and Hirschsprung's disease

4.3.2 Complex Neurocristopathies Associated with HD

HD is a simple neurocristopathy and also a member of complex neurocristopathies associated with nonneoplastic and neoplastic conditions. Neurocristopathies reported to be associated with HD include Waardenburg syndrome type 4 (Waardenburg-Shah syndrome), neuroblastoma, multiple endocrine neoplasia (MEN) type 2, congenital central hyperventilation (Ondine curse), Yemenite deaf-blind hypopigmentation syndrome, black locks-albinism-deafness syndrome, piebaldism, neurofibroma, and Riley-Day syndrome (familial dysautonomia syndrome) [12–14].

1. Waardenburg-Shah syndrome

   Waardenburg syndrome (WS) is the most frequent genetic condition combining pigmentary anomalies and sensorineural deafness. WS is 1of 40,000–50,000 live births and 2–5% of all congenital deafness. WS can cause hearing loss and changes in coloring of the hair, skin, and eyes. Although most people with WS have normal hear-

ing, moderate to profound congenital hearing loss can occur in one or both ears. The pathogenesis is the absence of melanocytes of the skin and the stria vascularis of the cochlea [14]. WS is clinically and genetically heterogeneous. There are four recognized types, which are distinguished by their physical characteristics and sometimes by their genetic cause. WS1 is characterized by pigmentary abnormalities of the hair, including a white forelock and premature graying; pigmentary changes of the iris, such as heterochromia iridis and brilliant blue eyes; congenital sensorineural hearing loss; and dystopia canthorum. WS2 is distinguished from WS1 by the absence of dystopia canthorum. WS3 has dystopia canthorum and is distinguished by the presence of upper limb abnormalities. WS4 has the additional feature of Hirschsprung's disease and termed Waardenburg-Shah syndrome [15]. Prevalence of hearing loss among the different clinical types significantly differed (WS1, 52.3%; WS2, 91.6%; WS3, 57.1%; WS4, 83.5%) [16]. WS4 is genetically heterogeneous and is further divided into types 4A, 4B, and 4C based on their genetic cause. WS type 4A (WS4A) is caused by heterozygous or homozygous mutation in the endothelin-B receptor gene (EDNRB) on chromosome 13q22. WS4B is caused by mutation in the EDN3 gene on chromosome 20q13. WS4C is caused by mutation in the SOX10 gene on chromosome 22q13 [15]. This condition is usually inherited in an autosomal dominant fashion; however, some cases of type 4 appear to have an autosomal recessive pattern of inheritance.

2. Multiple endocrine neoplasia (MEN) type 2

MEN type 2 is classified into three subtypes based on their occurrence [17]. MEN 2A is caused by heterozygous mutation in the *RET* oncogene on chromosome 10q11 [18]. MEN 2A is defined by an age-related predisposition to medullary thyroid carcinoma (MTC, 70% by the age of 70 years), pheochromocytoma (PC, 50% of cases), and hyperplasia of the parathyroid glands (15–35%) [14]. MEN 2B is caused by heterozygous mutation in the *RET* gene on chromosome 10q11, and most patients (95%) carry a specific M918T mutation in exon 16 of the *RET* gene [19]. MEN 2B is an autosomal dominant hamartoneoplastic syndrome characterized by aggressive MTC without hyperparathyroidism, PC, mucosal neuromas, thickened corneal nerves, and characteristic physical features, including full lips, thickened eyelids, and high-arched palate. Marfanoid habitus are present on most affected individuals [19]. Ganglioneuromatosis of the buccal membranes and the gastrointestinal tract was also reported with MEN 2B [17]. MEN 2B is considered to be the most aggressive of the MEN 2 subtypes, with a median age of onset 10 years earlier than seen in MEN 2A and higher likelihood of metastases [17]. The third subtype of MEN 2 is familial MTC (FMTC) characterized by the presence of MTC in multiple family members (four or more) as its only disease phenotype [17]. FMTC occurs from mutation in the *RET* gene on chromosome 10 and can also be caused by mutations in the *NTRK1* gene located on 1q21–q22 [20]. FMTC is included in MEN 2A in the classification of *Online Mendelian Inheritance in Man* [18–20]. FMTC is generally considered the least aggressive of the three MEN 2 subtypes with a later onset than MEN 2A or 2B [17].

The *RET* mutations, which have been identified as carrying both a risk for HD and MEN 2, approximate the transmembrane domain of the gene (mostly C620R and occasionally C620S and rarely C620W). Although the majority of reports connect these two conditions with point mutations in the cysteine-rich *RET* area at the 620 position, other *RET* gene areas, e.g., C609, C611, and C618, have been reported as alternative sites [21]. The high frequency with which the C620 *RET* mutation occurs in patients with HD and MEN suggests the concept of the so-called "Janus gene" mutation in this position, which, like the Roman god of doorways, can face in both directions, i.e., activation (MEN/MTC) and inactivation (HD) [21]. Moore and Zaahl [21] proposed that establishment of "risk" by genetic testing of *RET*620 (Janus gene) has become a classic model of molecular medicine being integrated into patient care and offering rearranged during transfection-directed prophylactic surgical management of chemoresistant and radioresistant MTC with poor prognosis. Coyle et al. [22] reported a systematic review of 341 patients with HD or MEN 2A, who had a Janus mutation (C620, C618, C611, C609). Co-occurrence of HD and MEN 2A occurred in 84 cases (24.6%), HD alone in 64 cases (18.8%), and MEN 2A alone in 173 cases (50.7%). The most common mutation recorded was the C620 mutation [114 cases (48.1%)]. The proportion of cases of long-segment HD and total colonic HD is higher than that in the general population with HD in those with C620 and C618 mutations. In contrast, an association of HD and MEN 2B is only observed in a single case report. Romeo et al. [23] reported on a 3-year-old girl with HD and MEN 2B, who had a typical exon 16 (Met918Thr) mutation. She showed severe constipation with an onset at the first week of life and was diagnosed to have aganglionosis in the last 5 cm of the rectum. Ganglioneuromatosis was also found in the resected proximal sigmoid colon. She was diagnosed with MEN 2B 1 year after the surgery for HD. Rakover et al. [24] reported two siblings with HD in whom isolated familial MCT was diagnosed at the age of 16 and 19 years. HD was identified at the age of 1 year in both of them. Both underwent total thyroidectomy, and histological examination revealed bilateral and multifocal MCT. These two patients belong to a large family in whom another 12

affected members with MCT were found. Rakover et al. stated that, although this was the first report of an association between HD and familial MCT, familial occurrence of HD could be an early presentation of familial MCT either as the isolated form or as part of MEN 2.

MEN 2A, MEN 2B, and FMTC are cancer predisposition syndromes with an autosomal dominant mode of inheritance. Germline missense mutations of the *RET* gene have been identified in those conditions. Amiel et al. [14] raised the question of whether all individuals with HD, regardless of noncontributive family history, should be screened for *RET* exon 10 and 11 mutations to rule out cancer predisposition, because some families with both FMTC and MEN 2A presented germline *RET* mutation of the MEN 2A or FMTC type.

3. Neuroblastoma

Neuroblastoma (NB) is the most frequent solid tumor in childhood with an incidence of 1/10,000. The tumor can arise at any site of the sympathetic chain or the adrenal medulla, both of which originate from NCC. In some cases of familial NB, tumor predisposition segregates through generations with incomplete penetrance. NB is found associated with HD and congenital central hypoventilation (CCHS) in various combinations. In each combination, heterozygous mutations of the paired-like homeobox 2B gene (*PHOX2B*) on chromosome 4p13 have been identified [14]. Recently, Armstrong et al. have reported a child with CCHS and HD who had a *PHOX2B* polyalanine-repeat-expansion mutation (PARM) and developed high-risk neuroblastoma [25]. They emphasized the need to consider NB in patients with CCHS and the longest *PHOX2B* PARMs.

4. Congenital central hypoventilation syndrome (CCHS)

CCHS was initially termed Ondine curse and a rare, life-threatening condition characterized by abnormal ventilatory response to hypoxia and hypercapnia due to failure of autonomic respiratory control. Although CCHS is not a neurocristopathy due to the involvement of both the central and peripheral autonomic nervous system, CCHS is often included in the category of neurocristopathies [13, 14]. Haddad et al. first described three patients of whom two were sisters. All three died in the first few months of life. They showed a combination of failure of autonomic control of ventilation during sleep and HD [26]. Esophageal motility and control of heart rate were also markedly reduced. Neuropathologic studies postmortem showed no anatomic defect. This condition was termed Haddad syndrome after his name. Trang et al. [27] reported based on French CCHS registry that, of 70 CCHS patients, 9 had HD and 2 had HD and neural crest tumor, indicating that 16% of CCHS patients were associated with HD. Croaker et al. [28] reported with an analysis of 44 patients with HD and CCHS that the sex ratio of this condition was 1:1, although sporadic HD has a 4:1 male preponderance. In their series, equal numbers of males and females (eight each) had aganglionosis affecting the whole colon or ileum, and the four most severely affected HD patients extending into the mid-small bowel or more proximally were all boys. Their data that more than half (59%) of patients with CCHS and HD had aganglionosis extending into the small bowel indicated that HD is severe in this combination. Amiel et al. [14] noted in the review of HD genetics that *PHOX2B* on chromosome 4p12 is the disease-causing gene with de novo heterozygous mutation in the proband, the far most frequent being in frame duplication leading to polyalanine expansion in this combination. Tsoutsinos et al. [29] reported on 3-year-old boy with CCHS and HD, which required permanent atrial pacing for supraventricular arrhythmia. They suspected that inadequate central control of ventilation with decreased sensitivity to hypoxia and hypercapnia might be associated with the cardiac rhythm disturbances observed. Rohrer et al. [30] reported on a male patient with CCHS and HD, who was diagnosed with chemotherapy-resistant NB at the age of 5 months and was not rescued. They emphasized the importance of screening CCHS patients for associated malignant illnesses such as neuroblastoma and ganglioneuroblastoma at time of diagnosis. Szymońska et al. [31] also reported on a male baby with total colonic aganglionosis and poorly differentiated NB with multiple liver metastasis and CCHS, who died on the 50th day of life. This baby showed a non-PARMs—mutation deletion in exon 3 (c.699–706, del8) of the *PHOX2B* gene located on the chromosome 4p12. Missense, nonsense, or frameshift mutations in the *PHOX2B* gene result in nPARMs. While these mutations account for less than 10% of cases, they lead to a more severe phenotype and most aggravated clinical manifestations [31].

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Sacral Pathway Theory of Hirschsprung's Disease

5

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Abbreviations

E	Embryonic day
ENS	Enteric nervous system
HSCR	Hirschsprung's disease
NC	Neural crest
NCC	Neural crest cells

The main pathophysiological feature of HSCR is a functional obstruction caused by the narrowing of the distal colon due to the continuous absence of ganglion cells in the myenteric and submucosal plexus. The absence of ganglion cells in HSCR has been attributed to failure of neural crest cells, as first hypothesized by Okamoto [1]. The essential role of enteric neurons in peristalsis control is showed by bowel obstruction that occurs in aganglionic regions of patients presenting with HSCR [2–4]. The lesion extends toward the caudocranial direction with most of the aganglionic segment occurring in the hindgut. Despite the neuronal disorder in pelvic space, no abnormality was present in the pelvic nervous system. Although various types of HSCR exist, the lesion exists from the anus to the rectosigmoid in approximately 80% of patients with HSCR [5–8].

Huther [9] speculated that the lesion occurs due to abnormalities in the lumbosacral nervous system where the ganglion cells in the hindgut originate.

However, numerous studies have reported that majority of intestinal ganglion cells are formed by vagal neural crest adjacent to somite first to seventh migrating from the esophagus toward the rectum [10–12]. And some researches showed that truncal and sacral NCC population make smaller contribution to total numbers for enteric NCC [12–14].

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The enteric nervous system (ENS) is thought to derive from vagal and sacral neural crest cells (NCC) that migrate, proliferate, and differentiate into enteric neuronal cells and glial cells within the gut wall [15–20].

Yntema and Hammond [20] speculated on the origin of the ENS over 50 years ago. Using neural tube ablation models, they determined that its precursor derived from vagal NCC. About 20 years later, Le Douarin et al. established the origin of the NCC forming the ENS. Research using an avian model provided evidence of the contribution of the sacral NC to the hindgut ENS [12, 21, 22]. The quail-chick xenografting technique [23] used sections of neural tube isotopically transplanted from quail to chick embryos at the same stage of development.

Subsequent analysis of the development of the gut located the origin of ENS cells in the vagal region of the NC next to somites 1–7, which exist along the entire length of the gut. Further, the sacral NC caudal to the 28th pair of somites was also shown to contribute cells to the hindgut [10, 21].

Several authors have subsequently supported data concerning the contribution of the vagal NC [11, 24, 25]. However, due to some conflicting findings, the role of the sacral NC in ENS formation remained unexplained for a long time.

Evidence supporting the role of the sacral NCC in ENS development came from cell labelling studies that traced the development of sacral NCC in chicks using antibodies binding to migrating NCC [22]. Pomeranz et al. reported streams of immunopositive cells in the dorsal bowel by E4 and within the mesentery at E5, which give rise to the nerve of Remak and eventually encircle the hindgut. Vagal NCC does not colonize the hindgut in these periods, indicating that the labelled cells derived from the sacral NC [26].

On the other hand, some researchers reported that in hindgut transection experiments done prior to the arrival of vagal NCC, enteric neurons did not develop in cultured explants [27–29]. Similarly, in midgut transection experiments, when the bowel was severed in ovo prior to the arrival of the cra-

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niocaudally migrating vagal NCC [30], the hindgut remained aganglionic, suggesting there was no contribution to the hindgut from the sacral crest. These data suggested that sacral NC contributes to the ENS in the mammalian hindgut.

Young et al. [31] described the craniocaudal progression of vagal-derived enteric precursors along the gut using detailed cell labeling of migrating NCC. In their study, no caudocranial migration of ENS precursors that could be attributed to early migrating sacral NCC was observed.

Similar observations were made in cell tracing studies performed in chick [26] and mouse gut [32] using injections of cell tracers such as DiI or a replication-defective retrovirus. In these investigations, labelled cells were reported in the hindgut mesenchyme. Similar observations were made in cell tracing studies performed in chick [26] and mouse gut at E4 and E9.5, respectively, in periods prior to the arrival of vagal-derived cells into the caudal gut regions.

Although some observations of the early arrival of sacral NCC within the gut have been reported [22, 26, 32], studies using gut explant cultures failed to identify an early, migrating, sacral NC-derived contribution to the ENS.

These investigations also suggested that there was no contribution of sacral NCC to the ENS.

Some studies have shown that sacral NC-derived cells migrate from the neural plate and extraenteric pelvic ganglia in early development. Later these cells are able to colonize the gut and contribute to the ENS, coincident with the migration of vagal-derived NC cells [11–13, 31].

Other researchers have suggested that sacral NC invade the hindgut mesenchyme several days before the colonization of the hindgut by vagal NCC and contribute to the development of ENS [22, 26, 32, 33].

In the mouse, it is generally known that the ENS is derived from the vagal NC (somite 1st–5th), truncal NC (somite 6th–7th), and sacral NC (somites posterior to 28th). Vagal NCC delaminate from the neural tube around E8.5 and migrate in the ventromedial direction, reaching the foregut at E9–E9.5 [24, 34]. After this stage NCC become enteric NCC containing ENS progenitor cells that migrate craniocaudally to colonize the entire length of the developing gut. This process reaches completion by around E14.5–E15.5. Sacral NCC delaminate from the neural tube at E9–E9.5 [32] and migrate ventrally to form extrinsic pelvic ganglia adjacent to the hindgut. Sacral NC migrate from there into the gut to give rise to enteric neurons and glia. Sacral NCC only migrate into the hindgut upon arrival of their vagal counterparts [12, 13]. However, they do not rely on vagal NCC for hindgut colonization to occur, as seen in the fact that sacral NCC migrate into the gut and give rise to enteric neurons and glia in the most distal regions of the intestine even after ablation of the vagal NC [11, 13, 24, 34]. Also, a rapidly increasing number of undifferentiated NC markers are found prior to their entry into the gut, indicating the presence of a pre-enteric specified subset of NCC [34, 35].

Some researchers examining the craniocaudal migration of NCC in a murine embryological model of HSCR have reported that the slow migration of vagal NCC results in the failure of craniocaudal migration. Hao et al. [36] showed that many immature neurons also migrate in the craniocaudal direction albeit at a lower velocity and over limited distances compared to undifferentiated vagal NCC. Other numerous studies using mouse models have contributed to the understanding of the developmental origins of HSCR and genetic complexity of this disease [37].

The ENS in humans derives primarily from the vagal NC. In the human fetus, NCC appear in the developing esophagus at the fifth week of gestation and then migrate craniocaudally during the fifth to 12th weeks of gestation [1, 9, 38].

We performed a study of the etiology of congenital anomalies of enteric ganglia in rat and human embryos using an immunohistochemical technique involving monoclonal antibodies specific for NF. NF^+ cells were first detected in the foregut among undifferentiated mesenchymal cells, which were detected at E11 in rat and at embryonic week 4 in humans. Thereafter the craniocaudal migration of NF^+ cells became apparent in the midgut at E11–E14 in rat and at embryonic week 4–6 in humans. However, in the hindgut, NF^+ cells were detected in the rectum to the colon in a caudocranial migration in the midgut at E14–E15 in rat and at embryonic period week 7 in humans. NF^+ cells of the pelvic plexus were found aggregating in the dorsolateral to the rectal wall and closely adjacent to NF^+ cells within the rectum. These findings suggest that the nerve cells in the hindgut of mammals originate from a second source of the neural precursor cells in the sacral neural crest.

Later, Fujimoto et al. [39] reported NCC migration in the developing gut in human embryos using an NF antibody and found that the enteric ganglia originated from a single vagal NC cell. The dual origin of enteric neurons has been negated by these studies using both human and chick embryos. The vast majority of studies have revealed that vagal NCC provide the main source of enteric neurons, while sacral NC additionally innervate the distal bowel.

For the reasons mentioned above, sacral nerve pathway theory is not currently considered to be an adequate explanation of the main cause of HSCR.

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6 Vascular Abnormality and Ischemic Theory

Tomoaki Taguchi

6.1 Ischemic Theory

The pathogenesis of Hirschsprung's disease has been discussed whether intestinal ganglion cells fail to migrate or they successfully migrate but are later destroyed. The former is the "craniocaudal migration theory," and the latter is "ischemic theory."

The presence of "zonal aganglionosis" [1, 2], "acquired aganglionosis" [3, 4], and "acquired hypoganglionosis" [5] suggests the possibility of the local regression and atrophy of ganglion cells and supports "ischemic theory." Cannon and Burket reported that of the four basic tissues (muscle, nerve, connective tissue, and epithelium), the neural elements were most sensitive to a lack of oxygen and did not regenerate after anoxic injury [6]. They demonstrated that the optimum length of the time for temporary ischemia to destroy ganglion cells was 4 h. This observation supports the possibility that temporary ischemia caused focal regression of ganglion cells. Earlam originally proposed the "ischemic theory," in which atresia and stenosis were suggested to be caused by ischemia lasting for long periods, but temporary or mild ischemia has been shown to destroy ganglion cells without permanently damaging any other tissues [7]. "Ischemic theory" is summarized in Fig. 6.1.

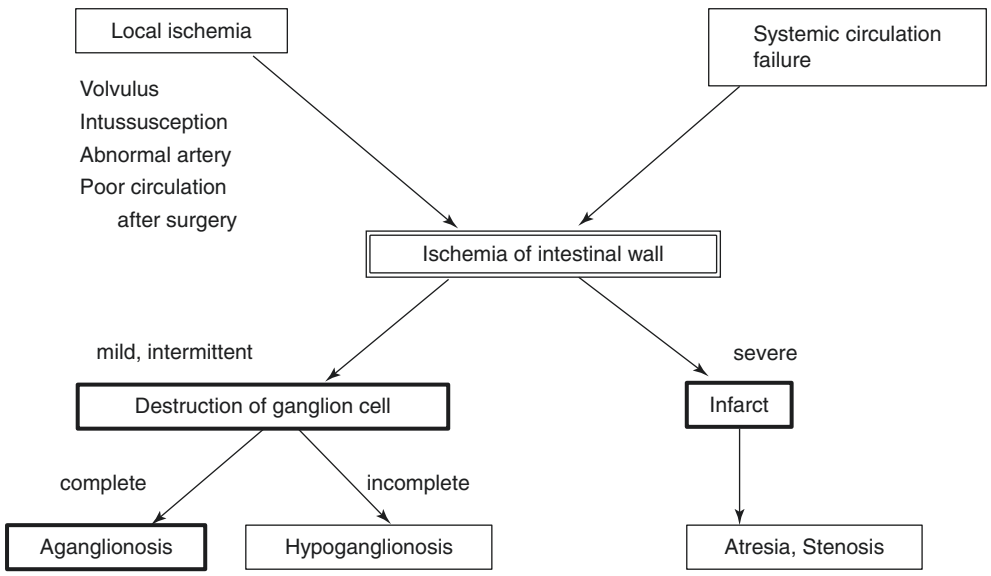

Fig. 6.1 Ischemic theory for intestinal obstruction

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6.2 Abnormal Arteries in Hirschsprung's Disease

Lister [8] reported vascular abnormalities in three of ten cases of Hirschsprung's disease. The abnormal vessels were found in the junctional zone between the expanded and unexpanded segments. Taguchi et al. [9] initially reported that abnormal arteries were present in 8 of 25 children (32%) with Hirschsprung's disease (Fig. 6.2). The histologic findings were similar to those seen in fibromuscular dysplasia with proliferation of smooth muscle cells in the thickened adventitia. These findings are compatible to those of "adventitial fibromuscular dysplasia" (Fig. 6.3). The abnormal arteries were located only in the transitional zone. Subsequently, Cohen et al. [10] reported that two of five cases of acquired aganglionosis following surgery for Hirschsprung's disease showed focal subendothelial thickening of blood vessels and an increase of fibrous tissue in the submucosa. Furthermore, Taguchi et al. [11] demonstrated that abnormal arteries were found in the intestines of 17 of 62 patients (27%) with Hirschsprung's disease. The incidence of abnormal arteries in each type of aganglionosis was as follows: 25% (13 of 51) in short-segment aganglionosis, 0% (0 of 6) in long-segment aganglionosis, and 80% (4 of 5) in total colon aganglionosis. The older the patients were at the time of resection, the higher the incidence of abnormal arteries (<1 year old, 15%; 1–3 years old, 38%; >3 years old, 75%). The abnormal arteries were mostly located in the histological transitional zone. From these analyses, we proposed that in total aganglionosis, the abnormal arteries were present congenitally and caused the cessation of craniocaudal migration or the regression of ganglion cells in utero and in short-segment aganglionosis, the mechanical tension force in the transitional zone seemed to change the vascular wall of the artery.

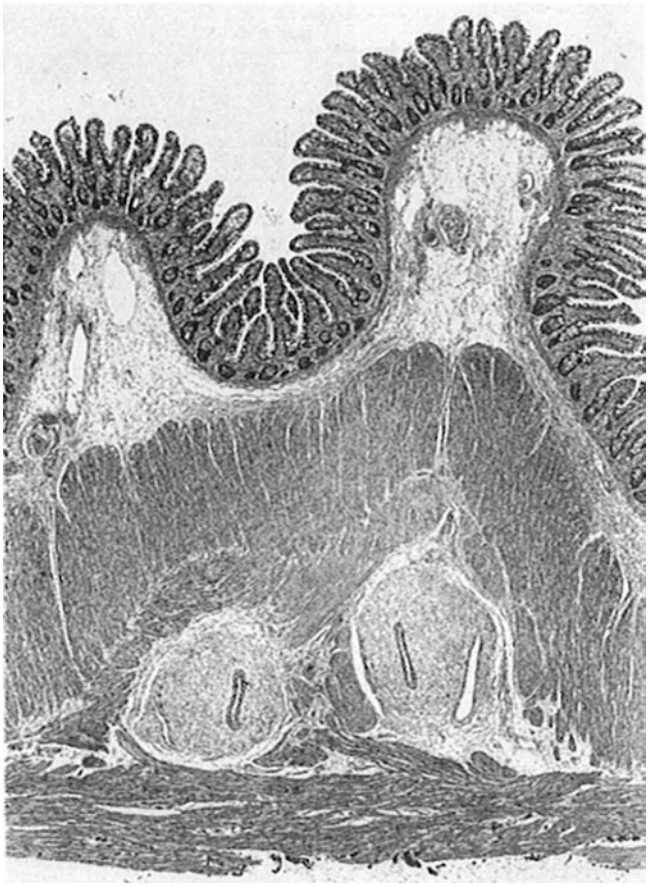

Fig. 6.2 Abnormal artery in Hirschsprung's disease. Abnormally shaped arteries are present in the proper muscle layer (×38 H.E. staining)

6.3 Abnormal Arteries in Allied Disorders of Hirschsprung's Disease

Udo et al. [12] found abnormal arteries in certain cases of isolated intestinal neuronal dysplasia (IND), Hirschsprung's disease-associated IND, as well as isolated HD. They showed that there were no abnormal arteries in control cases. Adventitial fibromuscular dysplasia shown by markedly increased collagen fiber expression around the external elastic lamina was found in 10/16 (62%) of the isolated IND cases and 4/11(36%) of the cases with IND associated with Hirschsprung's disease and 4/23 (17%) cases of isolated HD using van Gieson staining. None of the control specimens revealed AFMD. Increase of a-SMA (smooth muscle actin) immunoreactive filaments was detectable in the wall of submucous arteries in 9/16 (56%) isolated IND cases and in 2/11 cases (18%) with IND associated with Hirschsprung's disease. No a-SMA immunoreactivity around submucosal vessels was seen in isolated Hirschsprung's disease and controls. Increased a-SMA immunoreactive filaments and increased collagen fiber expression in submucosal vessels walls revealed clear findings of abnormal vasculature in the majority of the isolated IND cases. These findings suggest that abnormal vasculature may be a useful additional diagnostic feature in patients with IND. They found that the immunostaining of a-SMA was a useful tool for detecting abnormal artery and proposed that the presence of abnormal artery in submucosa was a useful tool of diagnosis of IND.

6.4 Experimental Study

The successful selective destruction of intramural ganglion cells by perfusion with Tyrode solution supported the ischemic theory [13]. However, Tibboel et al. [14] reported that, while temporary ischemia of the bowel frequently resulted in stenosis or atresia, the bowel tissue sections did not reveal any injury to the neurons or any aganglionosis in an experimental study. Currently, Bag et al. [15] reported that isch-

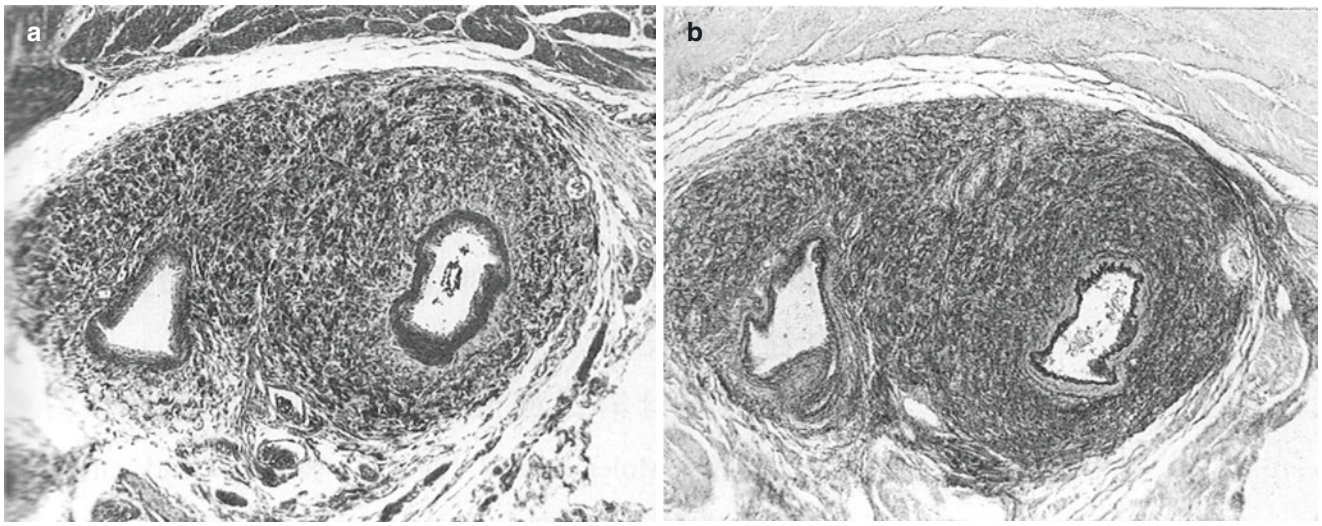

Fig. 6.3 Histological characteristics of abnormal artery. Left: Azan staining (×124), right: Elastica Van Gieson staining (×124). Adventitia of artery was thickened by the proliferation of smooth muscle fibers, collagen fibers, and elastic fibers. These findings are compatible to those of Adventitial fibromuscular dysplasia

Table 6.1 Abnormal artery in Hirschsprung's disease and allied disorders

Author	Type	No. of cases	Abnormal artery	%	Year	Reference
Lister	HD	10	3	30%	1966	[8]
Taguchi	HD	25	8	32%	1985	[9]
Cohen	Acquired HD	5	2	40%	1993	[10]
Taguchi	HD	62	17	27%	1994	[11]
Udo	IND	16	10	62%	2003	[12]
Udo	IND with HD	11	4	36%	2003	[12]
Udo	HD	23	4	17%	2003	[12]

HD Hirschsprung's disease; *IND* intestinal neuronal dysplasia

emia of the sigmoid colon resulted in hypoganglionosis instead of aganglionosis. They demonstrated that ischemia gave some damage to ganglion cells without any damages to other tissues.

6.5 Discussion

The presence of abnormal artery in Hirschsprung's disease and IND (Table 6.1) and the presence of cases of acquired aganglionosis or skip lesions have suggested that ganglion cells disappear after migration of neural crest cells. The abnormal expression of endothelin-B receptor gene in HD [16], the association of moyamoya disease and Hirschsprung's disease (our personal experience), and the association of myocardial disease and Hirschsprung's disease [17] might suggest the relation of cardiovascular abnormality and Hirschsprung's disease. Actually, the locus of neural crest is reported to be adjacent to the locus of cardiovascular structure. Abnormal genetic control of the neural crest may influence the vascular structure.

The presence of abnormal artery in the transitional zone suggests the following possibilities:

1. The craniocaudal migration of ganglion cells was interrupted by intestinal ischemia in the presence of abnormal arteries in utero.
2. An ischemic episode caused both the disappearance of neural cells and dysplasia of arterial wall.
3. The ganglion cells were destroyed by mild ischemia caused by the abnormal arteries.
4. The tension force of mechanical expansion resulted in a change in the vascular walls in the transitional zone.

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Incidence and Sexual Difference

7

Shigeru Ueno

In epidemiology, incidence is the probability of occurrence of a given medical condition in a population within a specified period of time. Hirschsprung's disease (HD) is a congenital condition, but a patient with the disease is noticed to have it at any time of his/her life, although it is mostly diagnosed in early infancy. Therefore, it is practically impossible to measure the incidence in a strict sense by estimating the number of patients in the entire population. Studies carried out to determine the incidence of HD reported it to be one loosely expressed simply as the number of new cases detected mostly in their early lives, during some time period, within specified area(s) or state(s). The incidence has been mostly expressed as a proportion or a rate with HD against live births.

In this chapter, many epidemiological aspects of HD are discussed. The incidences of HD per live births and its sexual differences are described based on the literature. Investigations about HD incidence have been reported from many states and areas around the world, and some have included chronological change of the incidence. Frequencies and male/female ratios according to the range of aganglionosis or transitional zone are discussed and summarized as well as familial incidences of the disease and sibling risks reported. Finally, frequency of patients with associated congenital condition, Down syndrome, is summarized.

7.1 Early Investigations on Incidence

Hirschsprung's disease (HD) is a congenital disease, which is named for Hirschsprung who described the clinical and pathological findings in newborns in 1886 [1–3]. Swenson and Bill established for the first time that the narrow segment is the cause of the disease and its resection can be the definitive treatments [4]. Diagnosis is based on the histological confirmation of the aganglionosis, and several pull-through procedures other than Swenson's have been proposed. Since then researchers have published the incidence of HD in many countries/states and areas using different methodologies.

These reports mostly included not only its incidence but gender difference and other demographic data. Diagnosis of HD is mostly made by histological examination after rectal biopsy in early infancy, but it is sometimes diagnosed later. When incidence of HD is discussed, it is important to recognize how patients with HD are accumulated and how a denominator is determined. Some reports identified patients as those experienced in a tertiary center, but others depicted cases from local or national databases. As for denominators, they described them from the livebirth data of the area or national census as well as newborn registries.

In 1963, Bodian and Carter reported the first large series of patients with HD to describe the incidence. Based upon 207 cases treated in The Hospital for Sick Children, United Kingdom (UK), the incidence was speculated to be between 1 in 2000 and 10,000 total births [5]. Passarge's study included patients seen at various hospitals in Cincinnati, the United States, and estimated the incidence as 1 in 5000 by using the registered births [6], and Mina and Guiney [7] reported the incidence of HD as 1 in 10,000 based on 53 patients treated in Irish children hospitals. Cram surveyed 65 cases experienced from 1951 to 1981 in Canada and concluded the incidence was 1/4000 live births [8]. These studies, however, concluded the incidence from records on patients drawn from a wide area with poorly defined populations and live births.

The first investigation about incidence in the well-defined geographical area is one by Orr and Scobie [9]. Their 103 patients with HD who were referred to a single surgeon at the Western General Hospital from southeast Scotland during the 30 years (1953–1982) were reviewed, and incidence was calculated based on Registrar General in Scotland. They concluded the incidence of the disease in the area as 1 in 4500 live births. From Baltimore of the United States, overall inci-

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dence of 1 in 5376 in a hospital-based series of 33 cases was reported [10]. From Vancouver, an incidence of 1 in 4417 in a cohort ascertained throughout British Columbia, Canada, was reported based on records of a health surveillance registry and 156 cases treated divided by live births from Statistics Canada [11]. Many textbooks and literatures describe the incidence of HD as about 1 in 5000 live births based upon above mentioned reports from the United Kingdom and North America.

7.2 Incidences Around the World

The first Japanese nationwide survey was carried out by Ikeda and Goto by questioning all major institutions and collected 1628 patients in a 5-year period (1978–1982) [12]. They concluded the incidence as 1 in 4679 from the annual number of newborns. Suita et al. [13] repeatedly surveyed the Japanese patients by questioning at 1988–1992 and 1998–2002 and collected 3852 cases combined with Ikeda's survey. The calculated incidences were 1 in 5544 and 5343 during the two eras which is consistent with those of previous surveys and those reported from countries with more Caucasian people inhabited. However, report from Denmark indicated Danish HD incidence the lowest ever estimated as 1 in 7165 live births from 207 cases over 20 years (1960–1980) [14].

From Oman the incidence of HD as 1 in 3070 was reported from data of 85 children between 1989 and 1994 divided by 261,000 live births among Omani nationals [15]. Even higher incidence was reported from the US Associated Pacific Islands based on 14 patients' demographical distribution and islands' births during a 9-year surveillance (1994–2002) [16]. The incidence in Tasmania was also high as 1 in 3429 estimated from 14 patients less than 15 years of age diagnosed between 1998 and 2005 [17] and that from Alaska was 1 in 3333 from 36 infants diagnosed between birth years 1996 and 2002 [18].

7.3 Recent Studies on Incidence

More recent studies carried out in Europe as similar population-based investigations indicated somewhat lower incidence than in Asian countries [19, 20], while a study from Utah of the United States demonstrated the incidence is like the latter [21].

In the North of England (UK) study, 105 cases extracted from cases encoded by ICD-10 as Hirschsprung's disease (Q431) from the Northern Congenital Abnormality Survey and validated against Hospital Episode Statistics were divided by the total number of registered births to the Office for National Statistics (ONS), and they estimated the incidence as 1.63 per 10,000 or 1 in 6129 live births (95% confidence interval, 1.33–1.98) [19]. Most recently published report which utilized data of patients up to 6 months of age registered to the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System estimated the incidence as 1.8 per 10,000 live births (95% CI 1.5 to 1.9) or 1 in 5671 [20].

On the other hand, Taguchi et al. reported the fourth nationwide survey in 35 years in Japan with 1087 cases collected divided by live births from the annual report from the Ministry of Health, Labour and Welfare in Japan and estimated incidence of 1 in 4895 [22]. In Taiwan, 629 cases encoded by ICD-9-CM as Hirschsprung's disease (751.3) or megacolon (564.7) in the Taiwan National Health Insurance Research Database and confirmed by the surgery code were identified. As a denominator, livebirth data obtained from Population Statistics of the Ministry of Interior in Taiwan were used, and they yielded the incidence as 2.2 per 10,000 live births or 1 in 4545 [23].

In Table 7.1, reported incidence data are summarized. The table includes countries/states or area(s) investigated, reported author(s), reported year with surveyed years, number of cases accumulated, case identification method(s), age of cases, incidence expressed both as 1 in estimated live births and estimated cases per 10,000 live births, and applied denominator for incidence calculations.

7.4 Chronological Change of Incidence

There are three reports which described incidences during different periods in the same country or area(s). As mentioned above, in Japan, four nationwide surveys in 35 years were carried out and revealed no chronological change of incidence [22]. On the other hand, in the North of England (UK) study, there was significant temporal increase from 1.26/10,000 in 1990 to 1994 to 2.29/10,000 in 2005 to 2008 [19]. Russell et al. [14] also reported significant increase of incidence in Denmark during their 20-year surveyed period (1960–1980), i.e., during 4- or 5-year period: 0.131, 0.132, 0.126, and 0.175/10,000, respectively.

7.5 Difference of Incidence Between Ethnic Groups and Other Factors

In Oman's investigation, incidences in different regions and within different tribes were also studied [15]. Estimated incidence among Omani population was 1 in 3070, while that of expatriate population was 1 in 4000. They also reported regional difference but no significant seasonal difference. Report from US Associated Pacific Islands showed great differences between islands [18]. Goldberg et al. reported the

Table 7.1 Summary of the reported incidence data

Country/state or institution(s)	Author	Reported year	Surveyed years	Case no.	Case identification	Case age	Denominator for incidence	Incidence		Ref.
								One/live births	Cases/10,000 live births	
Japan	Taguchi	2017	(2008–2012)	1087	Cases obtained from questionnaire to major institutions in Japan	All ages	Annual report from the Ministry of Health, Labor and Welfare in Japan	1/4895	2.04/10,000	[22]
UK and Ireland	Bradnock	2017	(2010–2012)	308	Cases identified by the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System	0–6 months	Reported live births by the Office of National Statistics	1/5671	1.76/10,000	[20]
Taiwan	Chia	2016	(1998–2010)	629	Cases encoded by ICD-9-CM as 751.3 or 564.7 in the Taiwan National Health Insurance Research Database		Population Statistics of the Ministry of Interior in Taiwan	1/4545	2.20/10,000	[23]
Utah (USA)	Downey	2015	(1997–2011)	129	Cases born in Utah and treated at a tertiary center in Utah	No mention	Utah Department of Health Center of Health Data, Office of Vital Records and Statistics	1/4788	2.09/10,000	[21]
North of England (UK)	Best	2012	(1990–2008)	105	Cases encoded by ICD-10 as Q431 from Northern Congenital Abnormality Survey validated against Hospital Episode Statistics	Less than 12 years	Total number of registered births to the Office for National Statistics (ONS)	1/6129	1.63/10,000	[19]
								Significant temporal increase		
Alaska (USA)	Schoellhorn	2009	(Birth years 1996–2002)	36	Cases encoded by ICD-9-CM as 751.3 matched with hospital discharged case records	Less than 1 year	Alaska Birth Defects Registry	1/3333	3/10,000	[18]
									5.6 for Alaska natives and 2.1 for non-natives	
Tasmania (Australia)	Koh	2008	(1998–2005)	14	Case records in a tertiary center in Tasmania	0–15 years	Australian Bureau of Statistics	1/3429	2.92/10,000	[17]
US Associated Pacific Islands (USA)	Meza-Valencia	2005	(1994–2002)	14	Case records in a tertiary center (TAMC) in Hawaii	0–2 years	International Data Base of the United States Bureau of the Census	1/3190	3.13/10,000	[16]
Japan	Suita	2005	(1998–2002)	1103	Cases obtained from questionnaire to major institutions in Japan	All ages	Live births not mentioned specifically	1/5343	1.87/10,000	[13]
	Suita	1997	(1988–1992)	1121	Cases obtained from questionnaire to major institutions in Japan	All ages	Live births not mentioned specifically	1/5544	1.80/10,000	

(continued)

Table 7.1 (continued)

Country/state or institution(s)	Author	Reported year	Surveyed years	Case no.	Case identification	Case age	Denominator for incidence	Incidence		Ref.
								One/live births	Cases/10,000 live births	
Oman	Rajab	1997	(1989–1994)	85		All ages	Live births not mentioned specifically	1/3070 (in Omani population) 1/4000 (in expatriate population) 1/3070 (in Omani population) 1/4000 (in expatriate population)	3.26/10,000	[15]
								Significant regional difference No seasonal difference significant regional difference No seasonal difference		
Denmark	Russell	1994	(1960–1980)	207	Cases with Danish origin: records from all over Denmark	0–20 years	National Danish Statistics	1/7165	1.40/10,000	[14]
British Columbia (Canada)	Spouge	1985	(1964–1982)	156	Case records encoded by ICD-9 as 751.3 in the British Columbia Health Surveillance Registry ascertained by Registry from different sources	0–30 years	Statistics Canada	1/4417	2.26/10,000	[11]
Children's Hospital in Pittsburgh (USA)	Garver	1985	(1970–1976)	31	Cases born in Allegheny County, PA, and treated at Children's Hospital of Pittsburgh and five large community hospitals	All ages	Census track figures for live birth within the county during the same period	1/4174	2.40/10,000	[24]
Japan	Ikeda	1984	(1978–1982)	1628	Cases obtained from questionnaire to major institutions in Japan	All ages	Live births not mentioned specifically	1/4697	2.13/10,000	[12]
Johns Hopkins University (USA)	Goldberg	1984	(1969–1977)	33	Cases encoded by ICD-8 as 751.2 born in Baltimore City and County, MA, ascertained by hospital records and death certificates	0–9 years	Number of live births during 1969–1977	1/5376	1.86/10,000	[10]
Southeast Scotland (UK)	Orr and Scobie	1983	(1953–1982)	103	Cases records born in south east Scotland	0–30 years	Registrar General in Scotland	1/4500	2.22/10,000	[9]
Canada	Cram	1982	(1951–1981)	65	Case records seen and treated in the three Saskatoon hospitals in Canada	All ages	Live births not mentioned specifically	1/4000	2.50/10,000	[8]
Hospitals in Cincinnati (USA)	Passarge	1967	(1958–1964)	38	Case records in hospitals in Cincinnati	All ages	Registered births in Cincinnati	1/5000	2.0/10,000	[6]
The Hospital for Sick Children (UK)	Bodian and Carter	1963	(1948–1959)	207	Case records attending The Hospital for Sick Children	All ages	Live births not mentioned specifically	Between 1/2000 and 1/10,000 total births	1–5/10,000	[5]

ethnic difference in Baltimore Standard Metropolitan Area as nonwhite was higher than white and nonwhite males had the highest rate of 37.6/100,000 or 1 in 2660 [10] although a nationwide survey in the United States and Canada carried out in the 1970s showed the disease is equally prevalent in blacks and whites [25].

7.6 Sexual Difference

Even the earliest report in 1963 from The Hospital for Sick Children about patients with HD demonstrated the male predominance [5]. Table 7.2 summarized the representative papers which accumulated a considerable number of patients with HD from various countries and areas. Male to female ratios reported vary but they are mostly estimated between 2 and 4. The largest number of patients with HD accumulated was 4939 from Japan during the period from 1978 to 2012, and its male/female ratio was consistently from 2.9 to 3.4 [12, 13, 22]. The least male to female ratio reported is 1.74 from British Columbia with 156 cases treated during 1964–1982 [11]. The highest male/female ratio is reported as 3.9 from 487 cases treated in Children's Hospital in Pittsburg and The Hospital for Sick Children during 1950–1977 and from 103 cases treated in southeast Scotland during the 1953–1982 period [31].

7.7 Frequency of Types of Hirschsprung's Disease

Hirschsprung's disease (HD) can be best termed as congenital intestinal aganglionosis, and it has been known that the length of the affected intestine varies. The classification of HD is based upon the distance from the internal anal sphincter encompassed by the aganglionosis, which most accurately describes the pathology, and four distinct types of HD are most commonly discriminated [11, 33]. Short-segment or "classic type" HD involves the anus, rectum, and a portion of the sigmoid colon. Sometimes short-segment type is further divided into two subtypes, one which involves the portion of the rectum below the pelvic floor and the other which involves up to the sigmoid colon. Long-segment type involves proximal bowel beyond the sigmoid colon up to the ascending colon, but some authors consider long segment at or beyond the transverse colon because of the embryological background [31]. Total colonic aganglionosis (TCA) is another type which involves the entire colon and may also have a portion of the terminal ileum involved. When aganglionosis extends beyond the terminal ileum, it is sometimes called extensive aganglionosis. An entity of ultrashort Hirschsprung's disease was initially described by Davidson and Bauer [34] and has been used to define a spectrum of conditions with clinical presentation similar to Hirschsprung's disease but with the presence of ganglion cells on rectal biopsy, which suggest the aganglionic portion within the very limited portion of the rectum, some claimed distal third of the rectum or less [35]. Orr and Scobie reported patients with ultrashort HD as much as 15% [9]. The difference between ultrashort HD and internal anal sphincter achalasia (IASA) is discussed in Chap. 41.

Frequencies of each subtype have been described in most papers which accumulated patients' data treated in the surgical sections, but classification of the disease varies between authors. Table 7.3 summarized frequencies of patients with distinct types, short-segment, long-segment, and total colon aganglionosis as well as aganglionosis which involves more extensive small intestine.

Patients with short-segment aganglionosis, which is defined as one limited to up to the sigmoid colon, have been reported to be the most common although frequencies somewhat vary from 57.7% to 87.1%. Patients with long-segment type are less frequent, and the reported frequencies range from 8.2% to 26.0%. Patients with the category of total colon aganglionosis or aganglionosis beyond the terminal ileum are least frequent, and its frequencies reported are less than 10% (Table 7.3).

The largest number of patients accumulated by a series of questionnaires in Japan had details of affected bowels of each patient [12, 13, 22]. They divided the extent of disease into five categories, which are rectum, sigmoid, long, total colonic, and extensive aganglionosis. Frequencies of patients with each category are consistent within four periods except in the last survey. According to the report by Taguchi et al., frequency of patients with aganglionosis limited within the rectum was 11.1%, while that of the previous three periods were around 25% [22]. Since patients with short-segment aganglionosis reportedly consisted of around 80% of all patients in all four periods, it may have become difficult in recent years to determine the exact extent of the aganglionic segment between the rectum and the sigmoid colon because of changing operative procedure.

7.8 Sexual Difference of Patients with Distinctive Types of Hirschsprung's Disease

It has been consistently reported in a large series of patients with HD that male preponderance tends to decrease with increasing length of the aganglionic segment. Male to female ratios of the whole series of patients with HD are summarized in Table 7.2. Details of those of patients with each subtype HD are summarized in Table 7.3. Male/female ratios of patients with short-segment HD have been reported to be from 3.4 to 5.4 while those of patients with longer than total colon affected to be around 2.0.

Table 7.2 Summary of male/female ratios of considerable number of patients reported

Country/state or institution(s)	Author	Reported year	Surveyed years	Case no.	Sexual difference	Ref.
Japan	Taguchi	2017	(2008–2012)	1087	2.9:1	[22]
UK and Ireland	Bradnock	2017	(2010–2012)	308	3.3:1	[20]
Taiwan	Chia	2016	(1998–2010)	629	2.38:1	[23]
Northwestern Tanzania	Mabula	2014	(2008–2013)	110	3.6:1	[26]
North of England	Best	2012	(1990–2008)	105	2.0:1	[19]
University Child Hospital Charles De Gaulle of Ouagadougou (CHUP-CDG) (Burkina Faso)	Bandré	2010	(2001–2007)	52	3.3:1	[27]
Tasmania	Koh	2008	(1998–2005)	14	3.7:1	[17]
US Associated Pacific Islands (USA)	Meza-Valencia	2005	(1994–2002)	14	3.7:1	[16]
Japan	Suita	2005	(1998–2002)	1103	3.0:1	[13]
		1997	(1988–1992)	1121	3.4:1	
Australia	Singh	2003	(1997–2000)	126	3.3:1	[28]
Oman	Rajab	1997	(1989–1994)	85	2.9:1	[15]
Hanyang University Hospital (South Korea)	Jung	1995	12 years	137	3.6:1	[29]
Children's Hospital of Michigan (USA)	Klein	1993	30 years	250	3.3:1	[30]
Children's Hospital in Pittsburgh (USA) The Hospital for Sick Children (UK)	Badner	1990	(1950–1977)	487	3.9:1	[31]
Le Bonheur Children's Hospital, Memphis (USA)	Foster	1990	(1955–1980)	63	3.2:1	[32]
Japan	Ikeda	1984	(1978–1982)	1628	3.0:1	[12]
British Columbia (Canada)	Spouge	1985	(1964–1982)	156	1.74:1	[11]
		1985	(1952–1983)	178	1.87:1	
Children's Hospital in Pittsburgh (USA)	Garver	1985	(1950–1977)	134	3.5:1	[24]
Johns Hopkins University (USA)	Goldberg	1984	(1969–1977)	33	4.32:1	[10]
Southeast Scotland (UK)	Orr and Scobie	1983	(1953–1982)	103	3.9:1	[9]
Canada	Cram	1982	(1951–1981)	65	1.86:1	[8]
Surgical Sections of the American Academy of Pediatrics (USA, Canada)	Kleinhaus	1979	(1967–1977)	1196	3.8:1	[25]
The Hospital for Sick Children (UK)	Bodian	1963	(1948–1959)	207	3.6:1	[5]

Table 7.3 Summary of reported frequencies and male/female ratios of patients with distinctive types

Country/state or institution(s)	Author	Reported year (surveyed years)	Case no.	Short-segment aganglionosis		Long-segment aganglionosis		Total colonic aganglionosis		Extensive aganglionosis		Unknown	Ref.
				(%)	M/F ratio	(%)	M/F ratio	(%)	M/F ratio	(%)	M/F ratio	(%)	
Japan	Taguchi	2017 (2008–2012)	1087	74.1	No data	14.9	No data	7.9	No data	3.6	No data		[22]
UK and Ireland	Bradnock	2017 (2010–2012)	270	73.3	No data	22.2	No data	3.0	No data	0	No data	1.5	[20]
Japan	Suita	2005 (1998–2002)	1103	77.7	No data	13	No data	6.5	No data	2.9	No data		[13]
		1997 (1988–1992)	1121	78.3	No data	12	No data	4.5	No data	5.2	No data		
Australia	Singh	2003 (1997–2000)	126	60.3	No data	17.5	No data	5.6	No data	0	No data	16.7	[28]
Oman	Rajab	1997 (1989 –1994)	85	87.1	No data	8.2	No data	4.7	No data	0	No data		[15]
Japan	Ikeda	1984 (1978–1982)	1628	79.5	No data	12	No data	5.1	No data	3.5	No data		[12]
HanYang University Hospital (South Korea)	Jung	1995 12 years	137	83.2	3.4:1	13.9	3.8:1	2.9	M4:F0	0	No data		[29]
Denmark	Russell	1994 (1960–1980)	207	85.5	4.1:1	Descending colon 4.3% (M/F = 8:1) Transverse colon 4.3% (M/F = 2:1) Cecum or small intestine 4.3% (M/F = 1.25:1) Long segment total 13.0% (M/F = 2:1)							[14]
Children's Hospital of Michigan (USA)	Klein	1993 30 years	250	57.7	3.5:1	26.0	3.0:1	11.6	2.2:1	0	No data	4.8	[30]
Le Bonheur Children's Hospital, Memphis (USA)	Foster	1990 (1955–1980)	63	76.0	No data	13.7	No data	1.7	No data	8.6	No data		[32]
Children's Hospital in Pittsburgh (USA) The Hospital for Sick Children (UK)	Badner	1990 (1950–1977)	487	67.1 87.1[a]	No data 4.4:1	12.7 Long segment total 10.0%[b] (M/F = 1.9:1)	No data	3.5	No data	2.1	No data	2.9	[31]
Children's Hospital in Pittsburgh (USA)	Garver	1985 (1950–1977)	134	76.9	5.4:1	23.1	1.2:1	5.2	2.5:1	1.5	1:1		[24]
Southeast Scotland	Orr and Scobie	1983 (1953–1982)	103	81.6	No data	18.4	No data	4.9	1.5:1	0	No data		[9]
Surgical Sections of the American Academy of Pediatrics (USA, Canada)	Kleinhaus	1979 (1967–1977)	998	75	No data	17	2.8:1	Total colon + above 8% (M/F = 2.2:1)					[25]
Chicago and Boston (USA)	Swenson	1975 (1947–1973)	478	72.8	No data	25.3	No data	1.9	No data	0	No data		[36]
The Hospital for Sick Children (UK)	Bodian	1963 (1948–1959)	207	82.0	No data	17.0	No data	0	No data	1.0	No data		[5]

[a]Short segment is defined up to the descending colon in Badner's paper
[b]Long segment is defined beyond the transverse colon in Badner's paper

7.9 Familial Incidence of Hirschsprung's Disease

Even the earliest report by Bodian and Carter from the United Kingdom demonstrated familial incidence and calculated it as 7.9% and risk of a sibling to have HD to be 5.9% [5]. Table 7.4 summarized the reported incidences of familial HD and sibling risk in the literature. Reported familial incidences are less than 10%, and the highest incidence reported is 8.2% from Pittsburgh, the United States [31], and the lowest is 2.9% from South Korea in recent series [29]. Familial transmission of the disease is much higher than the incidence of general population. Risks of having a sibling with HD are reported ranging from 1.8% to 5.9%.

As for the type of HD and familial incidence, a higher incidence of familial involvement in patients with long-segment type was reported as early as in 1967 by Passarge [6]. He also reported two of the six with long segment had affected siblings. Moore et al. [37] reported that 72% of the non-familial HD and only 39% of the familial group had rectosigmoid disease. They also reported that aganglionosis extended beyond the rectosigmoid in 61% of the familial group as opposed to 27% of the non-familial group, and a significantly higher number of total colonic aganglionosis were noted in those with a family history. Badner et al. subdivided all cases with aganglionosis at or beyond the transverse colon to be long segment and the rest of the cases to be short one. Calculated familial risk to have HD indicated there is increased risk in cases with aganglionosis extending beyond the sigmoid colon from 3% to 17% [31].

7.10 Frequency of Hirschsprung's Disease Associated with Down Syndrome

Chromosomal anomalies have been identified in children with Hirschsprung's disease (HD). Trisomy 21, known as Down syndrome (DS), is the most frequent abnormality

Table 7.4 Summary of reported incidences of familial Hirschsprung's disease and sibling risks

Country/state or institution(s)	Author	Reported year (surveyed year)	Case no.	Familial history (%)	Relative risk to sibling (%)	Ref.
Japan	Taguchi	2017 (2008–2012)	1087	7.1%		[22]
Japan	Suita	2005 (1998–2002)	1103	6.0%		[13]
		1997 (1988–1992)	1121	2.8%		
Hanyang University Hospital (South Korea)	Jung	1995 12 years	137	2.9%		[29]
South Africa	Moore	1991 34 years	370	4.0%	2.8%	[37]
Children's Hospital in Pittsburgh (USA) The Hospital for Sick Children (UK)	Badner	1990 (1950–1977)	487	Short (rectosigmoid) 3% Long (beyond transverse) 17%	4%	[31]
Children's Hospital in Pittsburgh (USA)	Garver	1985 (1970–1976)	134	8.2%	3.7%	[24]
Japan	Ikeda	1984 (1978–1982)	1628	3.0%		[12]
Johns Hopkins University (USA)	Goldberg	1984 (1969–1977)	33	9.0%		[10]
Southeast Scotland (UK)	Orr and Scobie	1984 (1953–1982)	103	6.0%	2.1%	[9]
Surgical Sections of the American Academy of Pediatrics (USA, Canada)	Kleinhaus	1979 (1967–1977)	798	7.0% Short (rectosigmoid) 6% Long (left, transverse, right) 7% Total colon + small bowel 21%		[25]
Hospitals in Cincinnati (USA)	Passarge	1967 (1948–1966)	63	6.3% Long (extending from the rectum to beyond the hepatic flexure) 6/63 (9.5%)	2.8% Short (1/57) (1.8%) Long (2/6) (33.3%)	[6]
The Hospital for Sick Children (UK)	Bodian	1963 (1948–1959)	207	7.9%	5.9%	[5]

Table 7.5 Summary of reported frequencies of patients with Hirschsprung's disease and Down syndrome

Country/state or institution(s)	Author	Reported year (surveyed year)	Case no.	Down syndrome (%)	Ref.
Japan	Taguchi	2017 (2008–2012)	1087	12.1	[22]
UK and Ireland	Bradnock	2017 (2010–2012)	308	8.9	[20]
Taiwan	Chia	2016 (1998–2010)	629	1.9	[23]
Utah (USA)	Downey	2015 (1970–2011)	404	1.7	[21]
Meta-analysis	Fiedmacher and Puri	2013 (1920–2008)	12225	7.8	[38]
North of England (UK)	Best	2012 (1990–2008)	105	10.0	[19]
University Child Hospital Charles De Gaulle of Ouagadougou (Burkina Faso)	Bandré	2010 (2001–2007)	52	3.8	[27]
USA	Cleves	2007 (1993–2002)	6117 (non-DS:5515) (with DS:602)	1.4 DS odds radio 103.6	[39]

associated with HD. There have been many reports about the incidence of HD and DS, but Friedmacher and Puri [38] made a meta-analysis of incidence and outcome of patients with HD and DS. They collected 948 cases with DS among 12,225 HD patients from community- or population-based sources and concluded the incidence of DS in HD as 7.75% although the reported incidences varied widely ranging from 0.64% to 16.25%. They also reviewed the literatures reporting on DS cohorts with or without HD and found 761 HD cases among 28,614 DS and concluded the incidence of HD in DS patients is 2.66%. Cleves and others identified all infants with or without DS and calculated odds ratios for the association by using logistic regression models, and concluded that incidence of HD in DS infants has 103.6 times higher than that of HD in non-DS infants [39]. Table 7.5 summarized frequencies of patients with HD associated with DS reported around the world.

Chronologically, incidences of HD with DS were reported to be increased over 30 years in Japan up to 12.1%, and it was speculated to be attributed to the increase of maternal age [40]. On the other hand, the incidence of the association was reported to be only 1.8% in a survey in Taiwan from 1998 to 2010. Authors speculated the reason of the lower rate to be due to the Down syndrome screening program implemented from 2001 [23].

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Classification

8

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Hirschsprung's disease has been usually classified by the extent of the aganglionic segment. However, there are no unified classification criteria in the world yet. Generally, it is classified as "short-segment aganglionosis" when the aganglionic segment extends to the sigmoid colon; especially, the aganglionic segment extends only to the rectum under peritoneal reflection, which is termed as "rectal aganglionosis" (Fig. 8.1a), and extends to the sigmoid colon, which is termed as "rectosigmoid aganglionosis" (Fig. 8.1b); "long-segment aganglionosis" when the aganglionic segment extends beyond the sigmoid colon to the splenic flexure or transverse colon or ascending colon (Fig. 8.1c); and "total colonic aganglionosis" when the aganglionic segment extends beyond the cecum to the distal ileum (Fig. 8.1d), and "extensive aganglionosis" when the aganglionic segment extends to the jejunum (Fig. 8.1e). Almost 80% of the patients with typical Hirschsprung's disease have aganglionic segment limited to the rectum and the sigmoid colon [1–4]. Previous studies presented that rectal aganglionosis accounts for 5.7–14.6%, rectosigmoid aganglionosis accounts for 64.9–67.0%, long-segment aganglionosis accounts for 12.0–26.0%, and total colon aganglionosis accounts for 2.8–12.0% (Table 8.1) [1, 5–10]. Almost all studies were institutional experiences in North America or Europe; however, only Singh et al. presented the nationwide survey of Australia from 1997 to 2000 [10]. Table 8.2 shows the nationwide survey of Japan for four series from 1978 [11–13]. Total patients' number has been gradually decreased followed by the decrease of birth. Recent study presented that the percentage of rectal aganglionosis, rectosigmoid aganglionosis, long-segment aganglionosis, total colon aganglionosis, and extensive aganglionosis presented 11.1%, 63.1%, 14.9%, 7.9%, and 3.1%, respectively [13].

Of rectal aganglionosis, "ultrashort aganglionosis" was first described in 1958 as specific criteria by Davidson and Bauer [14], which was usually termed as rectal achalasia. Neilson et al. [15] reported that the patients with "ultrashort aganglionosis" presented with chronic constipation, the presence of ganglion cells on suction rectal biopsy at 3 and 5 cm, and no typical caliber change using contrast enema. The anorectal manometry presents failure of the anorectal reflex. Thus, anorectal manometry is the most useful examination to diagnose ultrashort aganglionosis.

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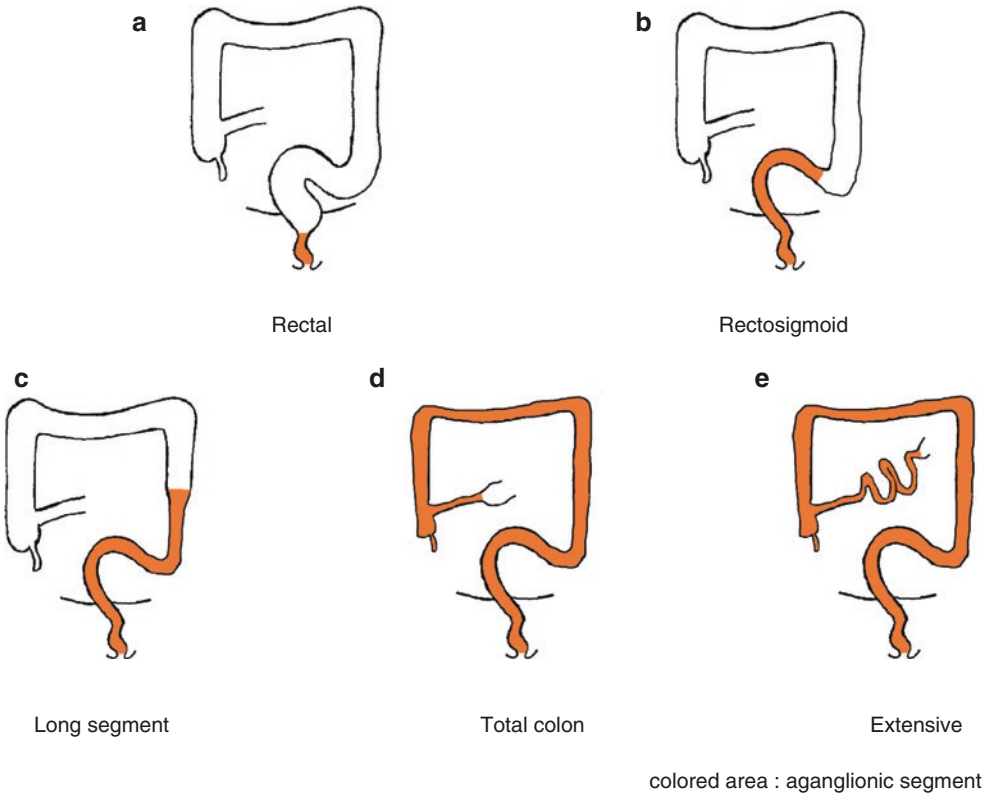

Fig. 8.1 Classification of Hirschsprung's disease

Table 8.1 Extent of aganglionic segment

Author	Year	Study period	Patients (*n*)	Type (%)				
				Rectal	Rectosigmoid	Long segment	Total colon	Extensive
Swenson [5]	1973	1950–1973	498	7.6	64.9	24.3	2.8	0.4
Kleinhaus [6]	1979	1975–1976	998	74.0		18.0	8.0	
Orr [7]	1983	1953–1982	103	14.6	67.0	18.4	0	0
Sherman [8]	1989	1973–1985	880	9.7	64.9	22.7	2.7	0
Klein [9]	1993	1960–1989	250	58.0		26.0	12.0	0
Singh [10]	2003	1997–2000	105	5.7	66.6	21.0	6.7	
Menezes [1]	2006	1975–2003	259	80.7		12.0	7.3	0

Table 8.2 Extent of aganglionic segment (according to the nationwide survey in Japan)

Author	Year	Study period	Patients (*n*)	Type (%)				
				Rectal	Rectosigmoid	Long segment	Total colon	Extensive
Ikeda [11]	1983	1978–1982	1628	25.7	53.8	12.0	5.1	3.5
Suita [12]	2005	1988–1992	1121	25.6	52.7	12.0	4.5	5.2
		1998–2002	1103	25.7	51.9	13.0	6.5	2.9
Taguchi [13]	2017	2008–2012	1087	11.1	63.1	14.9	7.9	3.1

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Symptom

9

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9.1 Introduction

Hirschsprung's disease (HD) is characterized by an aganglionic segment with enteric ganglion cells absent congenitally. In the aganglionic segment, peristaltic movement of the intestine is disturbed, thereby producing symptoms of bowel obstruction, such as delayed passage of meconium, bilious vomiting, and abdominal distension. The extent of the aganglionic segment varies considerably among patients; 74.2% of HD patients have short segment HD (S-HD), where the aganglionic segment extends proximally from the anus to part of the sigmoid colon, while the remaining 25.8% of patients have long segment HD (L-HD), where the aganglionic segment extends proximally beyond the sigmoid colon [1]. There are two types of aganglionosis that involve the entire length of the colon: total colonic aganglionosis (TCA) and extensive aganglionosis (EA). TCA refers to aganglionosis involving the entire colon, extending <30 cm proximally from the ileocecal valve, and occurs in 7.9% of patients. In 3.1% of patients with EA, the aganglionic segment extends ≥30 cm proximally from the ileocecal valve [1]. Symptomatic presentation varies according to the length of aganglionic segment and even in patients with the same extent of the aganglionic segment.

In a European surveillance study of HD, 78.4% cases of HD were reported to be isolated HD, excluding those with chromosomal anomalies (9.9%), genetic syndromes (1.1%), or major structural anomalies, such as congenital heart disease (ventricular septal defect, atrial septal defect), respiratory system disorder, orofacial clefts, digestive system disorders (duodenal atresia, jejunoileal atresia, anorectal anomaly), abdominal wall defects, urinary system disorders (hydronephrosis, posterior urethral valve), hypospadias, hip dislocation, and musculoskeletal disorders (11.6%) [2]. The frequent association of Down syndrome (DS) with HD is well-known, and its rate of occurrence is reported to be 5.9–12.1% in HD patients [3–5]. Some HD patients are also complicated with rare syndromes (Mowat-Wilson syndrome [6], Fryns syndrome [7], Bardet-Biedl syndrome [8], and Goldberg-Shprintzen syndrome [9]) or congenital anomalies of the kidney and urinary tract (CAKUT) [10].

These previous findings show that the symptoms of complicated HD are significantly affected by associated chromosomal, genetic, and structural anomalies. The symptoms of complicated cases, such as the genetic aspects, neurocristopathy, enterocolitis, and differential diagnoses, will be described in subsequent chapters of this book. In this chapter, the symptomatic presentation of isolated HD patients and HD patients with DS is mainly described, especially the findings in the neonatal and infantile periods.

9.2 Symptoms

9.2.1 Delayed Passage of Meconium

It is well-known that a delayed passage of meconium after birth might be an initial sign of clinical problems related to the gastrointestinal tract, such as HD, meconium ileus, meconium plug syndrome, intestinal atresia, and functional constipation. As shown in Table 9.1, 96% and 99.8% of healthy full-term infants pass their first stool within 24 and 48 h of birth, respectively [11] (Table 9.1). The mean timing of meconium passage was reported to be 16.2 h after birth [12]. However, preterm neonates usually show a delayed passage of meconium. Even though the median timing of meconium passage in preterm neonates was also 16 h after birth, time to meconium passage was within 72 h of birth for 93.5% of preterm neonates [13]. The timing of meconium passage was inversely related to the gestational age [14]. Even though the passage of meconium was not affected by gender, weight, maternal age, or parity in term neonates [12], gestational age, time to the first enteral feeding, respiratory

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Table 9.1 Timing of meconium passage in term and preterm neonates

Author	Year	Country	Subject	Timing of meconium passage	Factors for delayed passage of meconium	Factors not affecting meconium passage
Okoro	2013	Southern Nigeria	100 newborns	16.2 ± 10.6 h (mean and SD)	None	Gender Weight Maternal age Parity
Ogala	1986	Nigeria	100 full-term newborn	6 h 56%, 12 h 81%, 24 h 96%, 48 h 99.8%	nd	nd
Gulcan	2006	Turkey	200 newborns born <37-week gestation	16 h (median) 93.5% within 72 h	Gestational age Time to first enteral feeding Respiratory distress syndrome Mother treated with $MgSO_4$ for tocolysis	nd
Weaver	1993	UK	611 preterm infant of birth weight less than 1850	<24 h 37% <48 h 57% (born <29 weeks), 66% (29–32 weeks), 80% (>32 weeks)	Postconceptional age at birth	nd

nd not described

Table 9.2 Timing of meconium passage in HD

Author	Year	Region	Timing of meconium passage
Bradnock	2017	UK and Ireland	24% <24 h 20% 24–48 h 38% >48 h 4.6% no spontaneous passage
Alehossein	2015	Iran	72% >48 h
de Lorijn	2007	Netherland	81% >24 h
Singh	2003	Australia	57% >24 h
Swenson	1973	USA	94% >24 h

distress syndrome, or treatment of mother with $MgSO_4$ for tocolysis affected the passage of meconium in preterm neonates [13]. The meconium of premature infants was suggested to be more viscous than that of term neonates due to a different composition of glycoprotein, saccharides, calcium, copper, iron, and phosphorus [15].

In HD, the passage of meconium was markedly delayed, as shown in Table 9.2 [16–20]. The ratios of HD patients who passed meconium within 24 h after birth ranged from 6% to 43% [16–19]. The ratio of HD neonates who passed meconium within 48 h after birth ranged from 38% to 72% [18, 20]. In a UK and Ireland study of HD, the ratios of patients who passed meconium within 24 h, between 24 and 48 h, within 48 h after birth were 24%, 20%, and 38%, respectively, and spontaneous passage was not observed in 4.6% of HD patients [18]. In the same study, 86.6% of the HD patients were full-term neonates, and 85.3% of the patients weighed more than 2500 g [18]. Therefore, a delay in meconium passage in term neonates weighing >2500 g should be considered as a representative sign of HD.

9.2.2 Abdominal Symptoms

Abdominal distension was the most frequent symptom of HD neonates, with a prevalence ranging from 65% to 93%, followed by bilious vomiting, non-bilious vomiting, lack of appetite, and constipation (Fig. 9.1 and Table 9.3) [17, 18, 20, 21]. However, the "classic triad" of bilious vomiting, abdominal distension, and delayed passage of meconium was found only in 26.2% infants [18]. Singh et al. [17] and Bradnock et al. [18] reported that the ratios of HD patients diagnosed in the neonatal period were 83.9% and 90.5%, respectively. However, Kleinhaus et al. [22] reported that a diagnosis in the neonatal period and at <3 months of age was obtained in 15% and 30% of patients, respectively. Similar results were also found in nationwide surveys conducted four times in Japan [1]. A diagnosis of HD in the neonatal period was achieved only in 38.8% of patients, and the age at the diagnosis was after the infantile period in 11.6% of patients in the most recent survey between 2008 and 2012 (Table 9.4). This probably means that enema, stimulation of the anus, a rectal examination, or metal bougienage of the anus after symptomatic presentation may lessen the exacerbation of abdominal distension, allowing patients to be managed conservatively as having chronic constipation. de Lorijn et al. [19] summarized the points of difference between chronic constipation and HD as follows: fecal incontinence, large stool size, stool-withholding behavior, abdominal fecal mass, and ampullary feces were common in chronic constipation, while abdominal pain and failure to thrive were more likely symptoms of HD. Regarding the findings on a physical examination, dilated ampulla on an anal examination was a

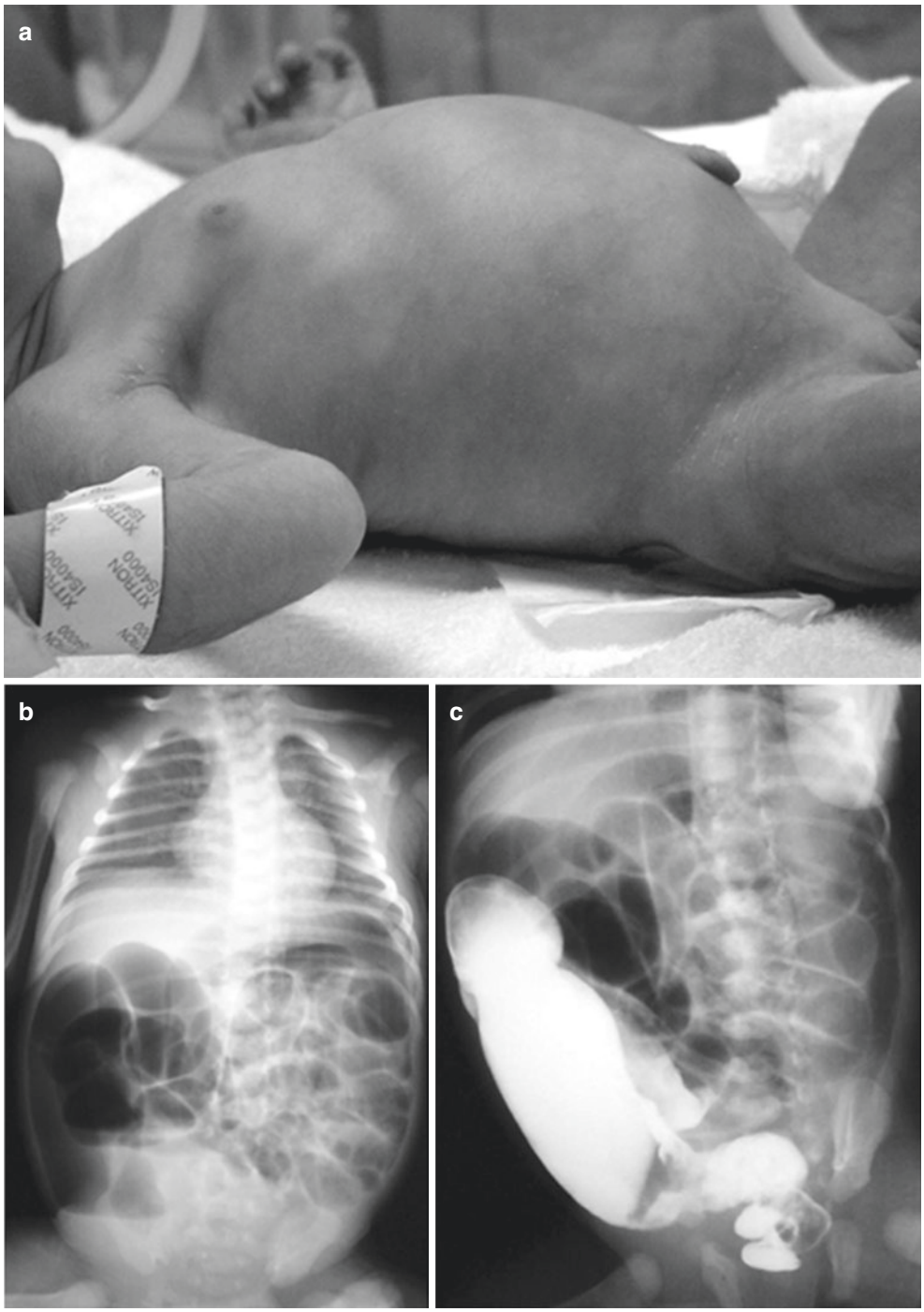

Fig. 9.1 Marked abdominal distension was observed in HD neonates on the first postnatal day (**a**). Abdominal plain film in the supine position (**b**) and barium enema (**c**) of this neonate. Abdominal X-ray showed diffuse dilatation of the small intestine and colon without colonic gas in the pelvic cavity (**b**). A transitional region was found in the sigmoid colon, suggesting rectosigmoid-type HD (**c**)

sign of chronic constipation, while narrow anorectum suggested HD.

It has been reported that one-third of HD patients present with diarrhea without obvious abdominal distension or vomiting, which indicate the presence of enterocolitis [19]. A digital examination often induces an explosive discharge of gas and liquid stool of a foul odor in cases of enterocolitis. Other symptomatic presentations of enterocolitis include rectal bleeding without diarrhea or explosive flatus. The incidence of preoperative enterocolitis is reported to range from 9.2% to 34.4% of cases, even in recent reports [1, 18, 23–25] (Table 9.5). The definition of HD-associated enterocolitis has not been conclusively established, which might be one of the reasons for the wide range of enterocolitis incidence.

A lack of recognizing HD may induce severe complications, such as early sudden neonatal death due to enterocolitis [26], lethal toxic megacolon [27], or intestinal perforation [28–30]. However, there are reports of HD neonates who

Table 9.3 Symptomatic presentations in HD neonates

Author	Year	Region	Presentation
Bradnock	2017	UK and Ireland	92.8% abdominal distension, 66.9% bilious vomiting, 19.3% non-bilious vomiting, 11.2% not opening bowels, 9.2% poor feeding, 9.2% suspected enterocolitis, 1.6% perforation
Alehossein	2015	Iran	77.7% abdominal distension, 72.2% lack of meconium defecation, 53% constipation
Singh	2003	Australia	76% abdominal distension, 69% vomiting, 57% delayed passage of meconium, 9.6% enterocolitis
Klein	1984	USA	65% abdominal distension, 58% emesis (35% bilious)

Table 9.4 Timing of the diagnosis in nationwide surveys conducted four times in Japan

	1978–1982	1988–1992	1998–2002	2008–2012
<1 month	48.7%	53.4%	40.1%	38.8%
<4 months	72.1%	76.0%	70.2%	72.5%
<12 months	83.4%	87.3%	95.3%	88.4%

Table 9.5 Incidence of preoperative enterocolitis in HD patients

Author	Year	Incidence of enterocolitis
Cheng	2017	34.4%
Taguchi	2017	17.6%
Bradnock	2017	9.2%
Imamura	1992	41.6%
Rescorla	1992	18.0%

present with pneumoperitoneum [31], diffuse intestinal pneumatosis [32], or sigmoid volvulus [33]. Such symptomatic diversity should be taken into consideration for understanding the rare symptoms of HD.

In preterm infants, symptoms of bowel obstruction are more frequently found due to prematurity itself and more likely to be caused by the frequent association of necrotizing enterocolitis, meconium plug syndrome, and functional constipation [2]. The precise reason for intestinal bowel dysfunction in preterm infants is unclear. Kenny et al. suggested the presence of delayed maturation of interstitial cells of Cajal for transient neonatal pseudoobstruction, which functions as a pacemaker cell of the intestine [34]. Similar findings of delayed maturation of interstitial cells of Cajal were also suggested in cases of meconium ileus without cystic fibrosis [35]. The prevalence of HD is significantly lower in premature infants (5%) than in term infants (50%) with obstructive symptoms [36]. Therefore, symptomatic preterm neonates need careful application of a further examination with barium enema or a suction rectal biopsy for a definite diagnosis.

9.2.3 Total Colonic Aganglionosis (TCA)

In a nationwide survey of 137 TCA patients in Japan, 67.4% of patients were diagnosed within the first month of life [37]. A similar figure of 64% was also reported in a single-institution survey of 25 TCA patients [38]. Bearing in mind the extensiveness of the aganglionic segment in TCA, these ratios of TCA patients diagnosed in the neonatal period are higher than those in S-HD, but seem to be much lower than expected. Furthermore, there are cases with much milder forms of presentation who were diagnosed at school age [39] or even in adolescence [40, 41]. It has been reported that 27% of TCA neonates present after the neonatal period, including those diagnosed after 6 months (14%) and 12 months (2%) [42].

While there is a strong male predominance of 4:1 or 3:1 in S-HD, there is only a weak male predominance of 1:1 or 2:1 in L-HD [43]. Badner et al. [44] reported the following characteristics of TCA patients: the risk of HD recurrence among siblings increased as the extent of aganglionosis increased from 4% in S-HD to 16% in TCA. A complex segregation analysis of HD family data suggested that the mode of inheritance was equally likely to be multifactorial or due to a recessive gene with very low penetrance in S-HD, while it was compatible with a dominant gene with incomplete penetrance in L-HD [44]. The association of DS was rare in TCA and mainly found in S-HD with a strong male predominance of 10.5:1 [44]. How these characteristics in TCA patients might induce later-than-expected presentation is unclear. However, such clear differences in the etiological background suggest a different pathophysiology in the aganglionic segment of TCA patients.

9.2.4 Impact of DS on Symptomatic Presentation

A systematic literature-based search for DS and HD revealed that the overall incidence of DS among HD patients was 7.32%, while the incidence of HD among 29,418 DS patients was 2.62% [45]. Potential disease-related RET mutations were identified in the intron region in 80% of the HD patients with DS investigated, suggesting a causal relationship of HD and DS [46]. Regarding the symptoms of bowel obstruction, the ratios of failure to pass meconium and bilious vomiting were similar between HD patients with and without DS. However, the association of preoperative enterocolitis and cardiac anomalies was significantly higher in HD patients with DS than in those without DS, while the associations of imperforate anus, orthopedic disorder, and pulmonary diseases were similar between HD patients with and without DS [47].

A total of 67% of HD patients with DS showed symptomatic presentation before 1 month of age [48]. On comparing

the patients by the presence of DS, symptomatic presentation was found in 94% of HD patients with DS within 2 weeks after birth, while only 70% of patients without DS presented before 1 month of age [49]. Therefore, symptomatic presentations are likely to be worsened by the association of DS in HD patients. Furthermore, postoperative complications, such as recurrent enterocolitis and soiling, are significantly more frequent in HD patients with DS [45].

9.3 Major Diseases Mimicking HD in the Neonatal Period

9.3.1 Food Allergy

Food allergy often causes obstructive symptoms mimicking HD [50–52]. Most of the food allergies are cow's milk allergy (CMA). Such patients usually start to show HD-like symptoms after the oral feeding of formula milk or the mother's ingestion of cow's milk. They often undergo barium enema for a differential diagnosis of HD. However, barium enema often shows irregularity of the wall, resembling the transitional region of HD (Fig. 9.2). Therefore, the history of abdominal symptoms in relation to milk ingestion must be carefully taken in cases suspected of CMA. Other diagnostic tools for diagnosing HD, such as a rectal mucosal biopsy and lymphocyte stimulation test for CMA, are necessary for a definitive diagnosis.

9.3.2 Congenital Hypothyroidism

Screening of hypothyroidism is useful for detecting congenital hypothyroidism before the symptomatic presentation of hypothyroidism, and a majority of infants with congenital hypothyroidism are symptom-free at birth. However, there are cases that present in the early [53] or late [54] neonatal period with abdominal distension and bilious vomiting. They show similar radiological findings to S-HD on barium enema. Early signs of hypothyroidism, such as prolonged unconjugated hyperbilirubinemia, poor feeding, hypotonia, and seizures, should not be missed before the grave complication of mental retardation occurs [54].

9.4 Closing

The symptomatic presentation of "isolated" HD neonates was mainly described in this chapter. The passage of meconium might be an important clinical sign of HD in term infants. However, in preterm infants, intestinal prematurity and frequently associated diseases often produce similar symptomatic presentations. The occurrence of enterocolitis and association of DS also affect the clinical picture. Of note, the symptomatic presentation of TCA might not be as severe as expected in cases of S-HD. To further clarify the symptomatic presentation of HD, genetic studies exploring the differences in the clinical presentation are necessary.

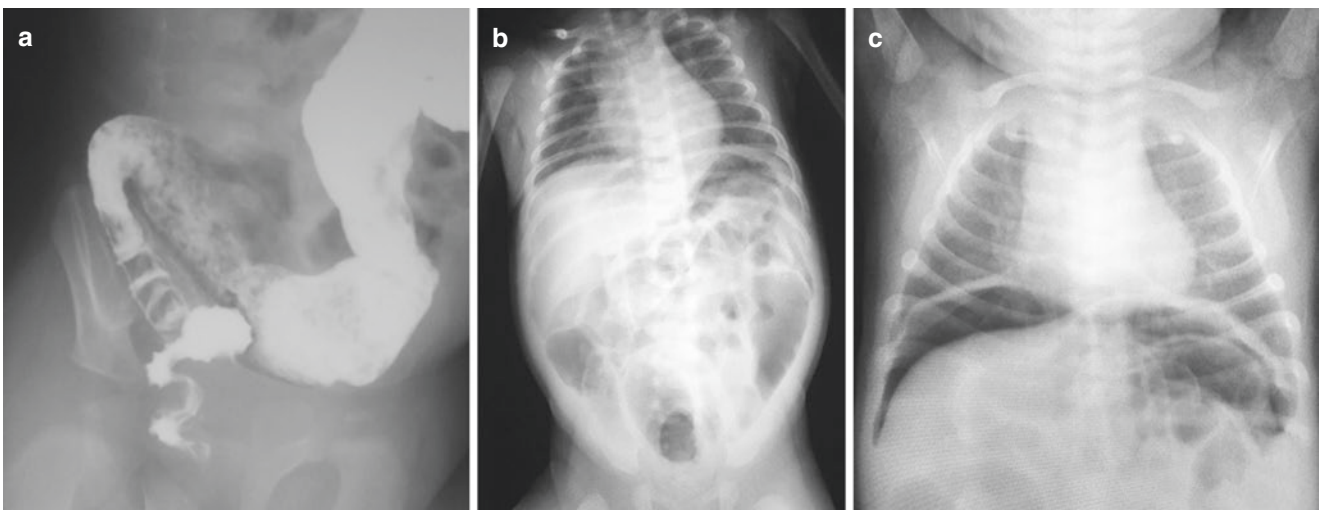

Fig. 9.2 Imaging studies of two patients with milk allergy. Barium enema in one patient (**a**) and plain X-ray of pneumoperitoneum in another patient: in the supine position (**b**) and the standing position (**c**). Note that the irregularity of the rectal wall and sigmoid colon resembles the aganglionic segment (**a**). In the supine position, gaseous dilatation of the small intestine and colon with a small amount of free air in the flank region (**b**) and subdiaphragmatic free air in the standing position (**c**) can be seen

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Hirschsprung's Disease Pathology

10

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10.1 Introduction

Although Harald Hirschsprung first described Hirschsprung's disease in 1888 [1], the pathological features were not understood until the 1940s, when Whitehouse and Kernohan [2, 3] demonstrated that aganglionosis within the distal colon or rectum was the cause of the functional obstruction.

In chronic constipation in childhood, diagnostic procedures such as radiographic contrast enema, anorectal manometry, and pathological approaches including acetylcholinesterase (AChE) histochemistry and rectal biopsy have been performed to differentiate idiopathic constipation from Hirschsprung's disease [4]. Although radiographic contrast enema is a useful tool for determining the distribution of lesions [5, 6] and a normal anorectal reflex in anorectal manometry is an adverse finding in Hirschsprung's disease, these methods have not been sufficiently developed to yield 100% diagnostic accuracy [6].

The pathological approach is a highly reliable and requisite method for diagnosis of Hirschsprung's disease [6]. However, it is sometimes difficult to distinguish Hirschsprung's disease from its allied disorders using only the pathological approach [7]. Therefore, to make a diagnosis of Hirschsprung's disease and its allied disorders, multilateral approaches based mainly on pathological diagnosis are needed.

The aim of this chapter is to discuss the histological features and frozen section diagnosis of Hirschsprung's disease.

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10.2 Pathological Definition

The key histological feature of Hirschsprung's disease is a congenital absence of ganglion cells in the continuous distal bowel beginning at the internal anal sphincter and extending proximally for varying distances [8–11].

10.3 Histological Features

Hirschsprung's disease is histologically characterized by the absence of ganglion cells (aganglionosis) in both the myenteric (Auerbach) plexus (between the smooth muscle layers of the gastrointestinal tract wall) and submucosal (Meissner) plexus (within the submucosa of the gastrointestinal tract wall) of a segment of the bowel [8–11]. The presence of hypertrophied, disorganized, and nonmyelinated nerve fibers of both adrenergic and non-adrenergic types is observed in the aganglionic segment; these abnormal fibers fail to properly innervate the intestinal smooth muscle [10–13]. In the aganglionic segment, fibro-collagenous fibers in the submucosal layer increase as time proceeds (Fig. 10.1).

In the transitional zone between normal ganglionosis and aganglionosis, the ganglion cells are immature and decreased in number, and hypertrophied and nonmyelinated nerve fibers are occasionally observed (Fig. 10.2). This transitional zone usually occurs over a short distance, but some patients have longer transitional zones than others [10].

Although mature ganglion cells are characterized by relatively large-sized rounded nuclei having coarsely granular chromatin, prominent nucleoli, and moderate-to-large amounts of amphophilic cytoplasm (Fig. 10.3), immature ganglion cells show small-sized nuclei, inconspicuous nucleoli, or small amounts of cytoplasm. In premature infants, it may be difficult to evaluate the immaturity of ganglion cells due to their relatively small size. Meanwhile, there are no definitive criteria in terms of numbers of ganglion cells to distinguish normoganglionosis from the transitional zone. In one previous morphometrical study, normal numbers of

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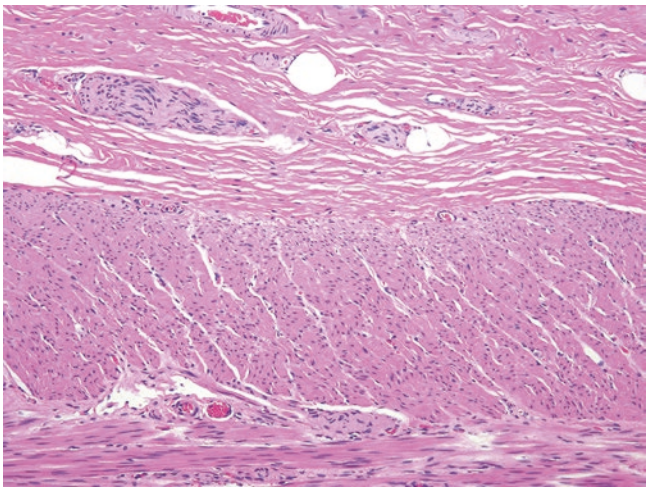

Fig. 10.1 Aganglionic segment. Some thickened nerve bundles in the submucosal and intramuscular layer are seen

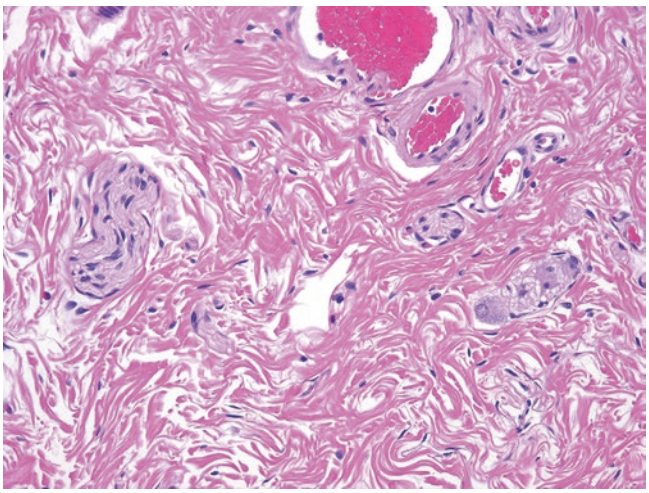

Fig. 10.2 Transitional zone. Although there are mature ganglion cells in Meissner plexus, thickened nerve bundles are scattered

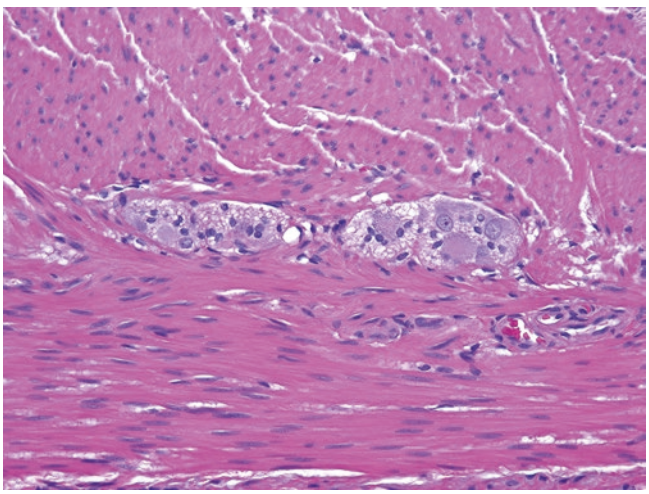

Fig. 10.3 Normoganglionic segment. More than one mature ganglion cells in one neural plexus is observed

ganglion cells of the intestine differed depending on age (<3 months, 117.9 ± 26.0/cm; 3 months–1 year, 63.3 ± 23.4/cm; 1–10 year, 64.8 ± 23.2/cm; >10 year, 38.6 ± 13.4/cm) and site (ileum, 84 ± 22.6/cm; transverse colon, 123.0 ± 24.3/cm; sigmoid colon, 137.3 ± 20.6/cm) [7], but the 50–100 ganglion cells per 1 cm of intestine reported by Taguchi et al. may provide an indication of the normal range in the neonatal bowel depending on the site or age.

10.4 Hirschsprung's Disease Form

Based on the extent and location of the aganglionic segment, several forms of the disease have been recognized [4, 10, 11, 14].

10.4.1 Short-Segment Form

Ultrashort form: The aganglionic segment is only a small area of the lower rectum, and this narrow segment is inconspicuous by radiographic contrast enema. The diagnosis of this variant can be missed if the biopsy is taken at too proximal point in the intestine.

Conventional short-segment form: The aganglionic segment involves several centimeters of the rectum and rectosigmoid.

10.4.2 Long-Segment Form

Conventional long-segment form: The aganglionic segment extends beyond the sigmoid or transverse colon.

Total colonic aganglionosis: The aganglionic segment is more extensive, involving most or all of the large bowel and up to 30 cm of the terminal ileum.

Extensive aganglionosis: The aganglionosis extends proximally more than 30 cm to the ileocecal valve.

10.5 Immunohistochemistry

Important diagnostic parameters of Hirschsprung's disease are numbers and distributions of the neural plexus, the existence or nonexistence of nerve fibers, and the numbers and maturity of ganglion cells in the neural plexus. However, it is difficult to evaluate these particulars using only HE staining. Immunoreactivities for some neural markers have the potential to become an ancillary parameter in the diagnosis of Hirschsprung's-related disease.

CD56, also known as the neural cell adhesion molecule (NCAM), is a homophilic binding glycoprotein located on the membranes of neurons and glia [15–18]. In the intestinal

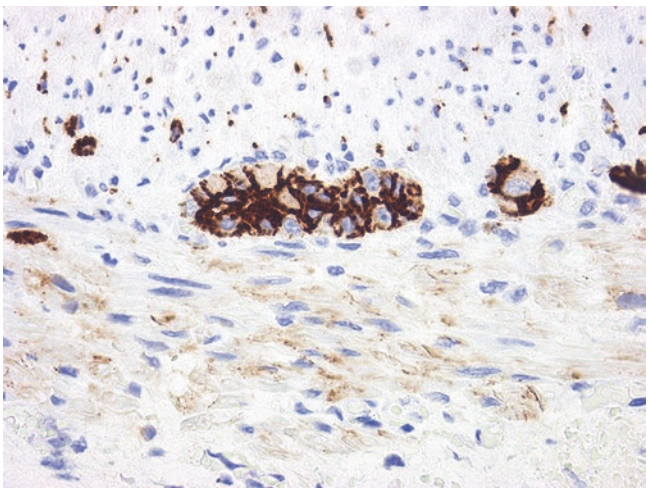

Fig. 10.4 All neural cells including neural fiber, enteric glia, and ganglion cells are positive for CD56

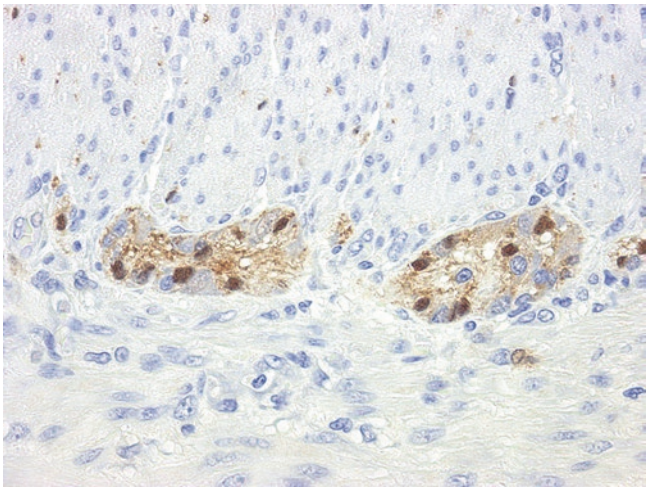

Fig. 10.5 Ganglion cells do not exhibit immunoexpression of S100 proteins

wall, all neural cells and networks are positive for CD56 (Fig. 10.4). Therefore, it is useful to understand the distributions of the neural plexus and nerve fibers.

The S100 proteins are a family of low-molecular-weight proteins and are characterized by two calcium-binding sites of the EF-hand type [19]. S100 proteins are normally present in cells derived from the neural crest (Schwann cells and melanocytes), chondrocytes, adipocytes, myoepithelial cells, macrophages, Langerhans cells, and dendritic cells. In the intestinal wall, neural fibers and enteric glia are positive for S100 proteins (Fig. 10.5). However, the ganglion cells do not exhibit immunoexpression of S100 proteins.

HuC/D, members of the Hu family, are the RNA-binding proteins that display neuron-specific expression and are involved in neuronal differentiation and the maintenance of the nervous system [20, 21]. In the intestinal wall, HuC/D

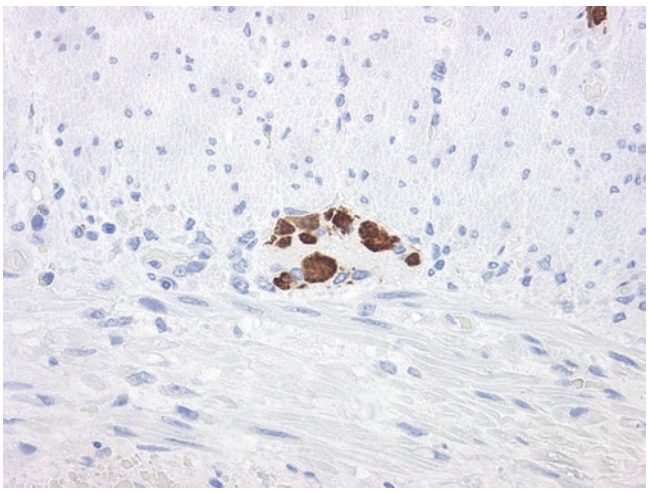

Fig. 10.6 Ganglion cells in the enteric neural plexus are positive for HuC/D

immunoreactivity reveals the ganglion cells, while the other neural cells and fibers do not show HuC/D immunoexpression (Fig. 10.6). It is thus useful to identify the numbers and sizes of the ganglion cells.

BCL-2 encodes an integral outer mitochondrial membrane protein that blocks the apoptotic death of some cells such as lymphocytes [22]. High levels of BCL-2 expression are maintained in sensory and sympathetic adult neurons [23]. In Hirschsprung's and its allied disorders, BCL-2 immunostaining reveals small or immature ganglion cells, but mature large neurons are negative or faintly stained for BCL-2 [24]. BCL-2 is the most valuable biomarker for discriminating immature small neurons [24].

Calretinin is a calcium-binding protein of 29 kDa that is a member of the family of so-called EF-hand proteins [25]. Calretinin is reported to be abundantly expressed in neurons. There is a lack of immunostaining for calretinin in aganglionic segments in patients with Hirschsprung's disease and in the nerve fibers in these areas, whereas both ganglion cells and nerve fibers show calretinin expression in ganglionic areas of Hirschsprung's disease and in the normal colon [26]. Although a clear distinction between transition zone tissue and normal tissue cannot be made using calretinin, it serves as a feasible fallback system in cases with inadequate biopsies that contain little or no submucosa [26].

10.6 Frozen Section Diagnosis

The transanal endorectal pull-through has been widely performed as a minimally invasive operative procedure to surgically correct the functional obstruction in Hirschsprung's disease. In such cases, intraoperative diagnosis of normoganglionosis in the frozen section is absolutely necessary.

Table 10.1 Pitfalls in the frozen section diagnosis

Surgical point
Full-thickness biopsy
Biopsy site: mesenteric side
Sample size: a length of at least 1 cm in the direction of the long axis
Pathological point
Maturity of ganglion cells
Absence of nerve bundles
Number of ganglion cells: 50–100 ganglion cells per 1 cm of intestinal wall

However, there are two pitfalls in the frozen section diagnosis: the first involves the site of intraoperative biopsy and the second involves the diagnosis of normoganglionosis (Table 10.1).

The transitional-aganglionic bowel junction on the mesenteric side tends to be more proximal than that on the antimesenteric side [27]. The circumferential distribution of ganglion cells in both the myenteric and the submucosal plexus in the transitional zone is uneven [28]. Even if a diagnosis of normoganglionosis is made based on intraoperative biopsy performed from the antimesenteric side, there remains the possibility of a transitional zone on the mesenteric side. Therefore, intraoperative biopsy should be implemented from the mesenteric side in frozen section diagnosis.

Checkpoints for diagnosis of normoganglionosis are the evaluations of maturity, the number of ganglion cells, and the presence or absence of nerve bundles. These assessment criteria have been previously noted. To this end, full-thickness biopsy is necessary to give an accurate diagnosis of normoganglionosis for several reasons. The transitional zone histologically shows heterogeneous maturation and numbers of ganglion cells. Seromuscular biopsy is not able to identify submucosal aganglionosis, hypoganglionosis, immaturity of ganglia, or nerve hyperplasia [6]. Moreover, a sample size with a length of at least 1 cm in the direction of the long axis is required for the evaluation of numbers of ganglion cells.

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Examinations for Diagnosis

11

Naoki Shimojima

11.1 Preface

Hirschsprung's disease may easily be suspected based on several characteristic clinical symptoms and physical findings, such as constipation starting early in life, delayed first passage of meconium, severe abdominal distension, etc. However, examinations are necessary for diagnosis, including a radiography, motility study, and pathological examination. The examinations are both qualitative and quantitative and aim at a definitive diagnosis and determination of the extent of aganglionosis.

This chapter includes a description of a radiological and motility study and confocal laser endomicroscopy, a novel method of visualizing the enteric nervous system.

11.2 Radiological Diagnosis

Constipation starting early in life, delayed first passage of meconium, and severe abdominal distension are characteristic findings in patients with Hirschsprung's disease. If these symptoms are present, an abdominal X-ray is usually performed as the first examination necessary for diagnosing Hirschsprung's disease. Distension of the colon and small intestine due to gas is a characteristic finding on X-ray, with the distal colon showing a gradually widening on the oral side. The absence of gas in the pelvis is another clue to the presence of Hirschsprung's disease as the collapsed distal colon usually does not contain gas (there are some exceptions). An X-ray film with contrast enema is recommended for neonates because distinguishing between small intestinal gas and large colon gas on X-ray may be difficult.

The contrast enema is the second radiological examination performed after the X-ray. The biggest difference between these two examinations is that the contrast enema can visualize the shape of the colorectum directly. The distal aganglionic segment in Hirschsprung's disease is visualized as a narrow segment. At the transition zone, the caliber widens, and the dilated oral segment can be seen containing a large quantity of gas and stool. This sudden widening of the caliber at the transition zone is called the "caliber change" and is very important for predicting the length of the bowel to be surgically resected. Depending on the location of the caliber change, the preoperative classification may be the short type at the lower rectum, the rectosigmoid type at the upper rectum to sigmoid colon, the long type at the descending to ascending colon, total colonic aganglionosis at the distal ileum, or extensive aganglionosis at the upper small intestine. The extent of the aganglionic segment determines the treatment strategy and even the long-term prognosis [1]. Sometimes, a caliber change is ambiguous, and repeated examination is necessary to obtain clearer findings.

The contrast enema is carried out by injecting a contrast medium into the rectum using a thin (8–10 Fr.) rubber tube. Assessment begins from the end of the rectum. The tip of a thin rubber tube with a bandage at 1 or 2 cm from the tip (Fig. 11.1) (rather than a rubber tube with a balloon) is placed in the anal canal. The contrast can be injected from the end of the rectum without leakage by inserting the tip of the tube into the anal canal and pushing it inward while injecting the contrast. A water-soluble contrast is the best choice for neonates.

Fig. 11.1 Tube for contrast study. Note the stopper close to the tip

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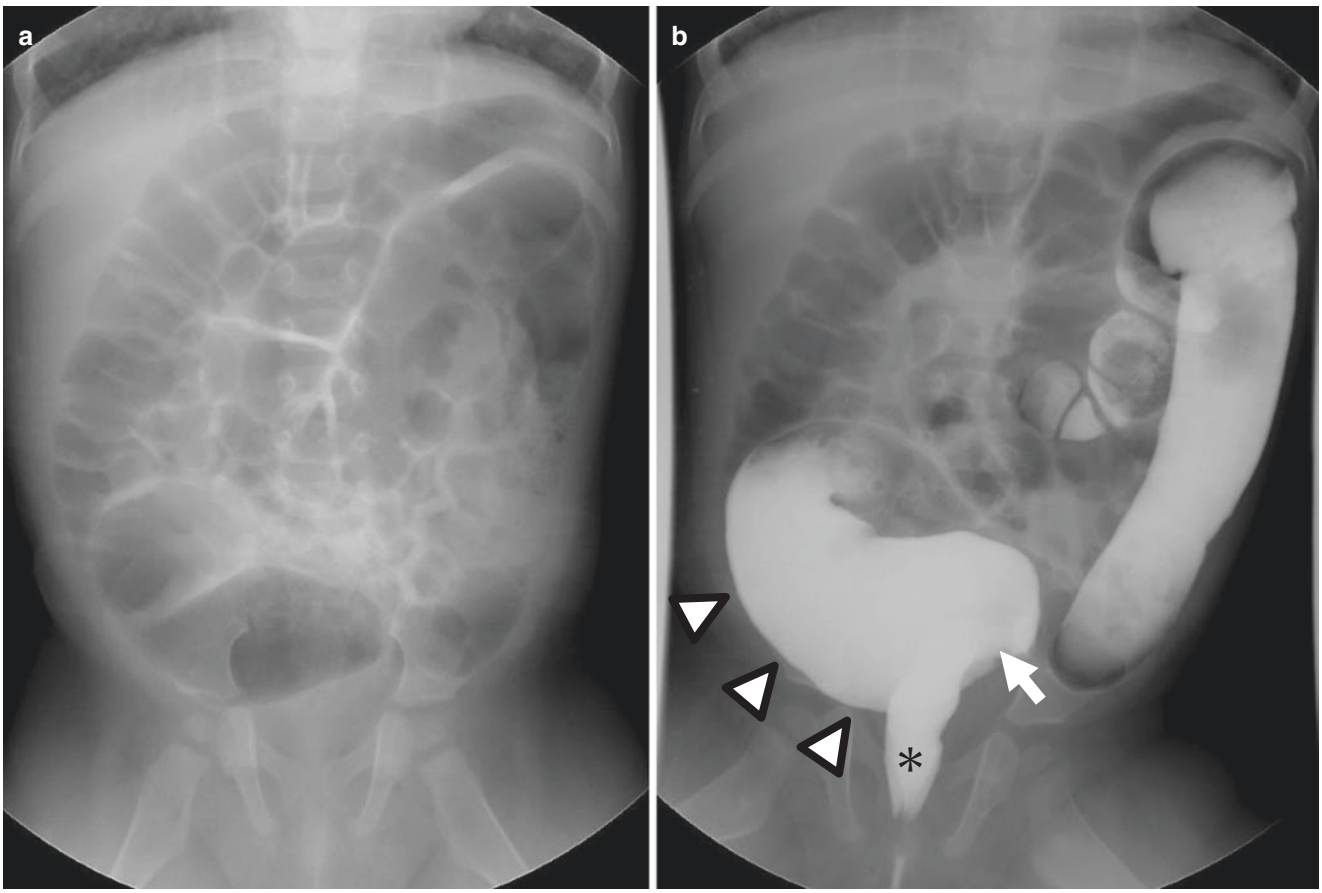

Fig. 11.2 (**a**, **b**) Short-type Hirschsprung's disease in an 11-month-old boy. (**a**) Abdominal X-ray showing diffuse intestinal gases. No gas is present in the pelvis. (**b**) Contrast enema shows narrow lower rectum (*) and gradually dilating upper rectum (△). The caliber change can be clearly seen (arrow)

The effect of rectal preparations such as the glycerin enema or washout by a rubber tube prior to a contrast study is controversial. The distended proximal bowel may be decompressed by these preparations, and the caliber change can become ambiguous. However, some studies have concluded that these preparations do not affect the diagnosis [2].

The X-ray and contrast enema findings can vary by the classifications mentioned above. Figures 11.2, 11.3, 11.4, 11.5, and 11.6 show some representative findings.

11.2.1 Short-Segment Aganglionosis

Figure 11.2a, b was taken from a patient with short-type Hirschsprung's disease accompanied by congenital heart disease and trisomy 21. Although constipation and abdominal distension were obvious from birth, passing of stool was made possible by routine glycerin enemas. These pictures were taken when the patient was 11 months old.

An abdominal X-ray showed diffuse dilated intestinal gas although no gas was observed in the pelvis. A contrast enema showed a narrow lower rectum (*) and gradually dilating upper rectum (Δ). The caliber change between these two segments can clearly be seen (arrow) and strongly suggests the diagnosis of Hirschsprung's disease. The dilated oral segment (the so-called megacolon) reaches the descending colon, and dilation of the small bowel is relatively mild.

11.2.2 Rectosigmoid Aganglionosis

Figure 11.3a, b was taken from a patient with typical, rectosigmoid-type Hirschsprung's disease on postnatal day 2. An abdominal X-ray clearly showed colonic and small bowel distention due to gas. A contrast enema showed a clear caliber change in the narrowing of the rectum (*) and the megacolon at the sigmoid colon (△). Stool can be seen in the descending colon (+). After this examination, the abdominal distension resolved after the gas and stool were evacuated by inserting a drainage tube into the anus.

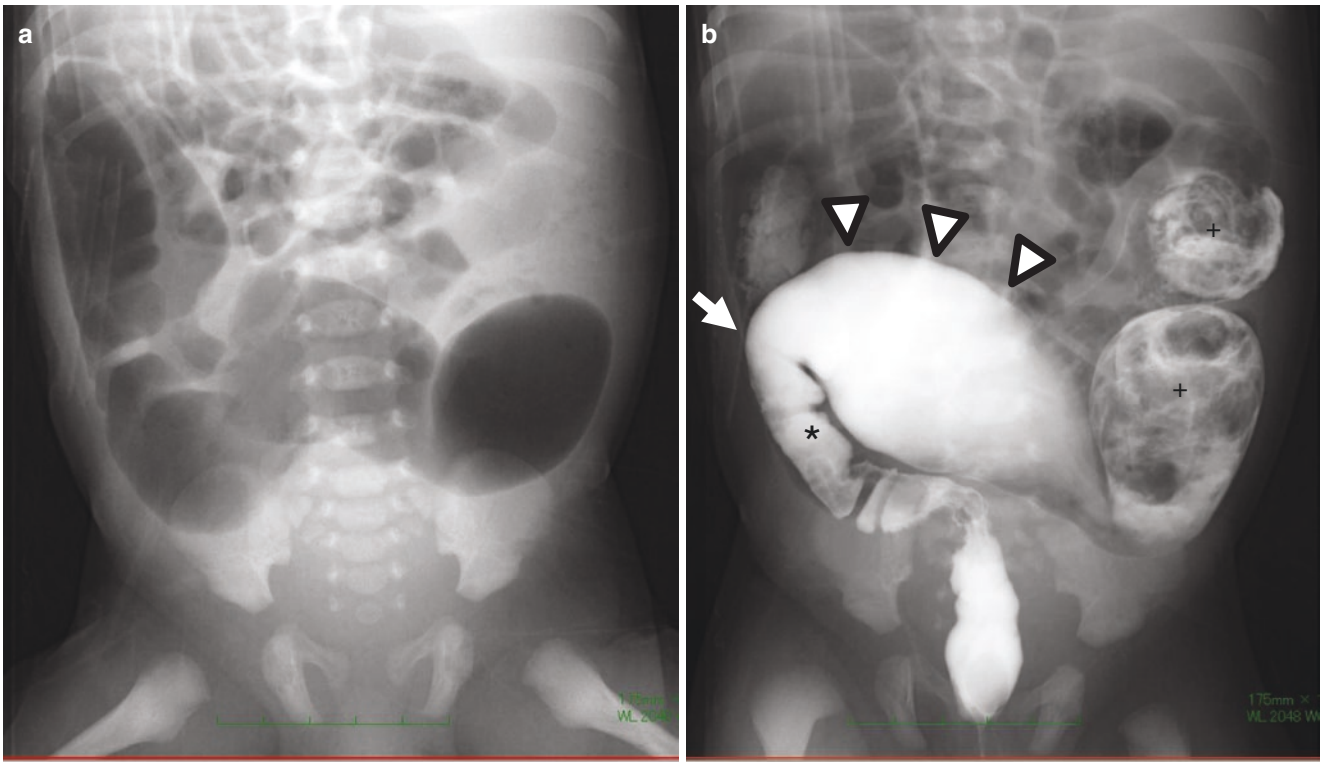

Fig. 11.3 (**a**, **b**) Rectosigmoid-type Hirschsprung's disease in a 2-day-old boy. (**a**) Abdominal X-ray shows obviously increased colonic gas and dilated small bowel gas. (**b**) Contrast enema showing narrow rectum (*) and megacolon at the sigmoid colon (△). The caliber change is clearly visible. Note stool impaction in the descending colon (+)

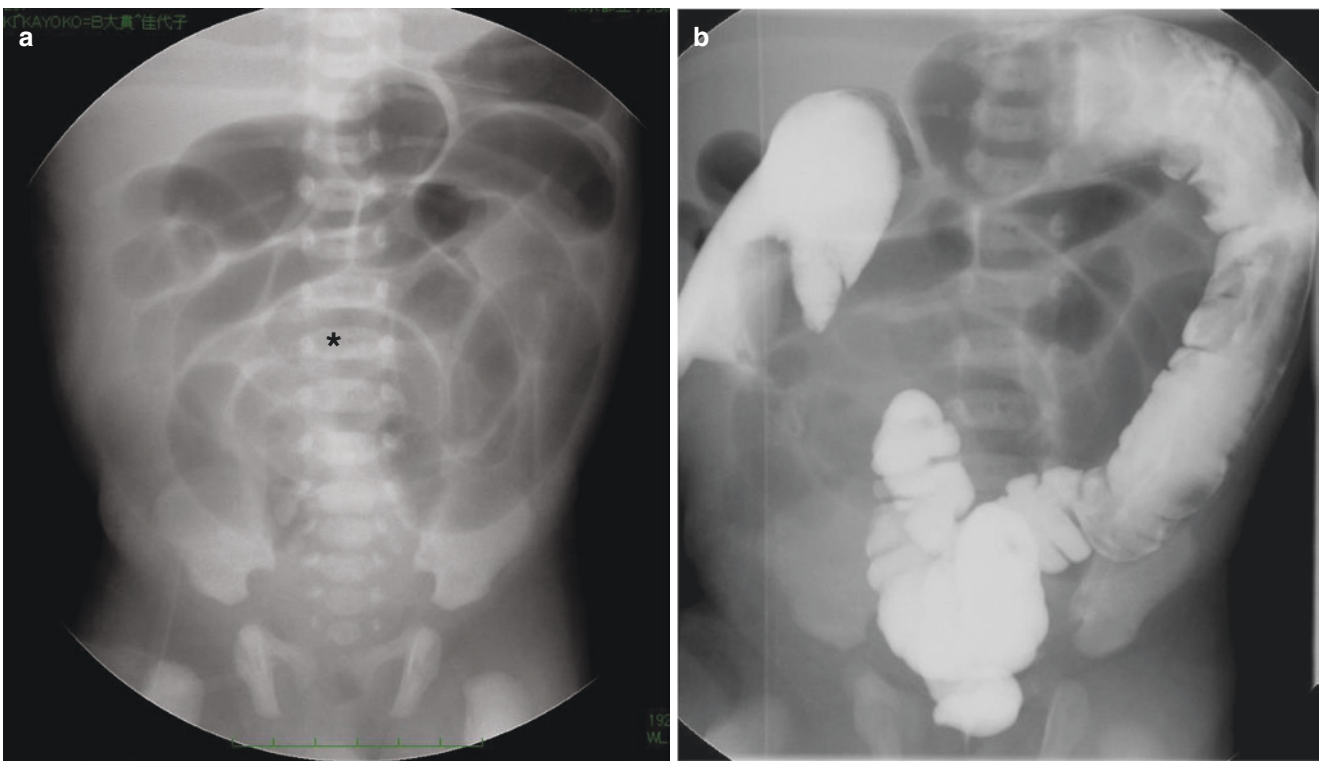

Fig. 11.4 (**a**, **b**) Long-type Hirschsprung's disease in a 2-day-old boy. (**a**) Abdominal X-ray diffusely showing distended loops of small bowel (*). (**b**) Contrast enema failed to show narrow segment in the distal colorectum. Transverse colon showed dilatation, but the caliber change was not clear

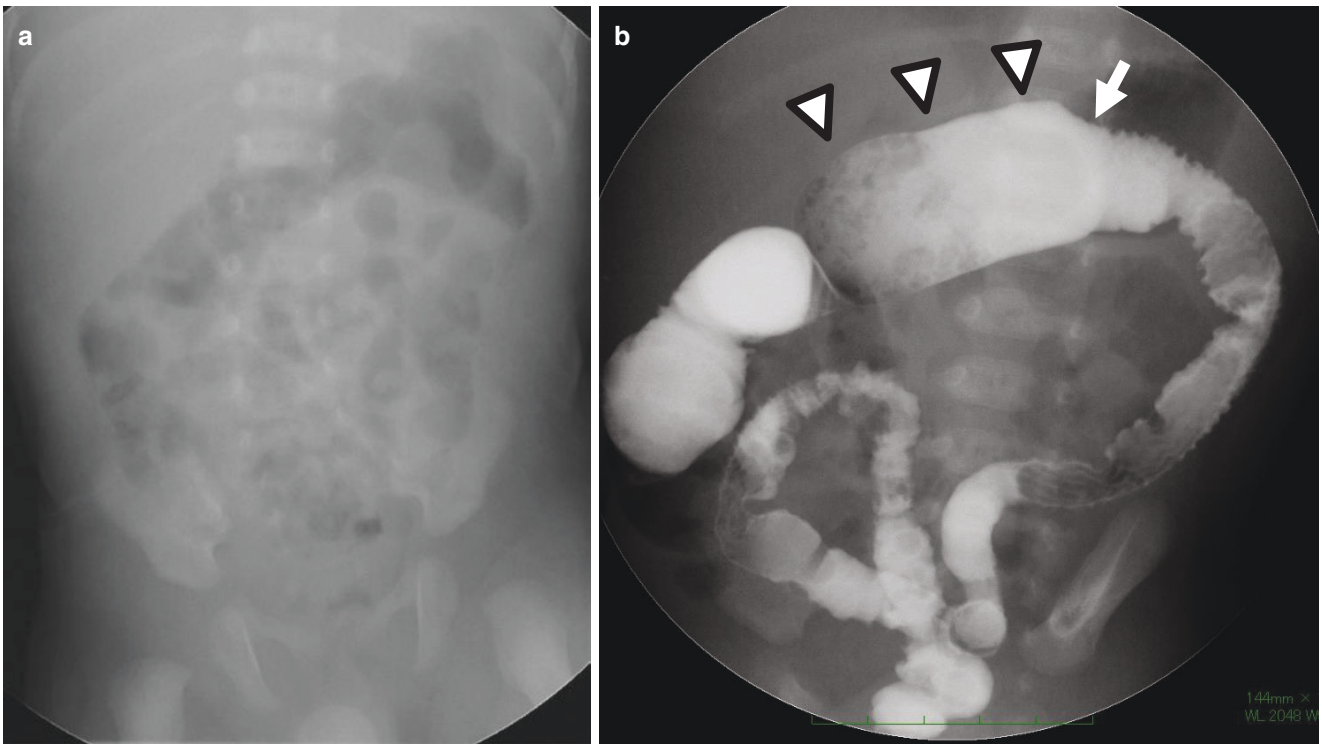

Fig. 11.5 (**a**, **b**) Same patient as in Fig. 11.4 at 25 days of life. (**a**) Dilation of small bowel disappeared. (**b**) Contrast enema showing caliber change at the transverse colon (arrow) with dilatation of the proximal colon (△)

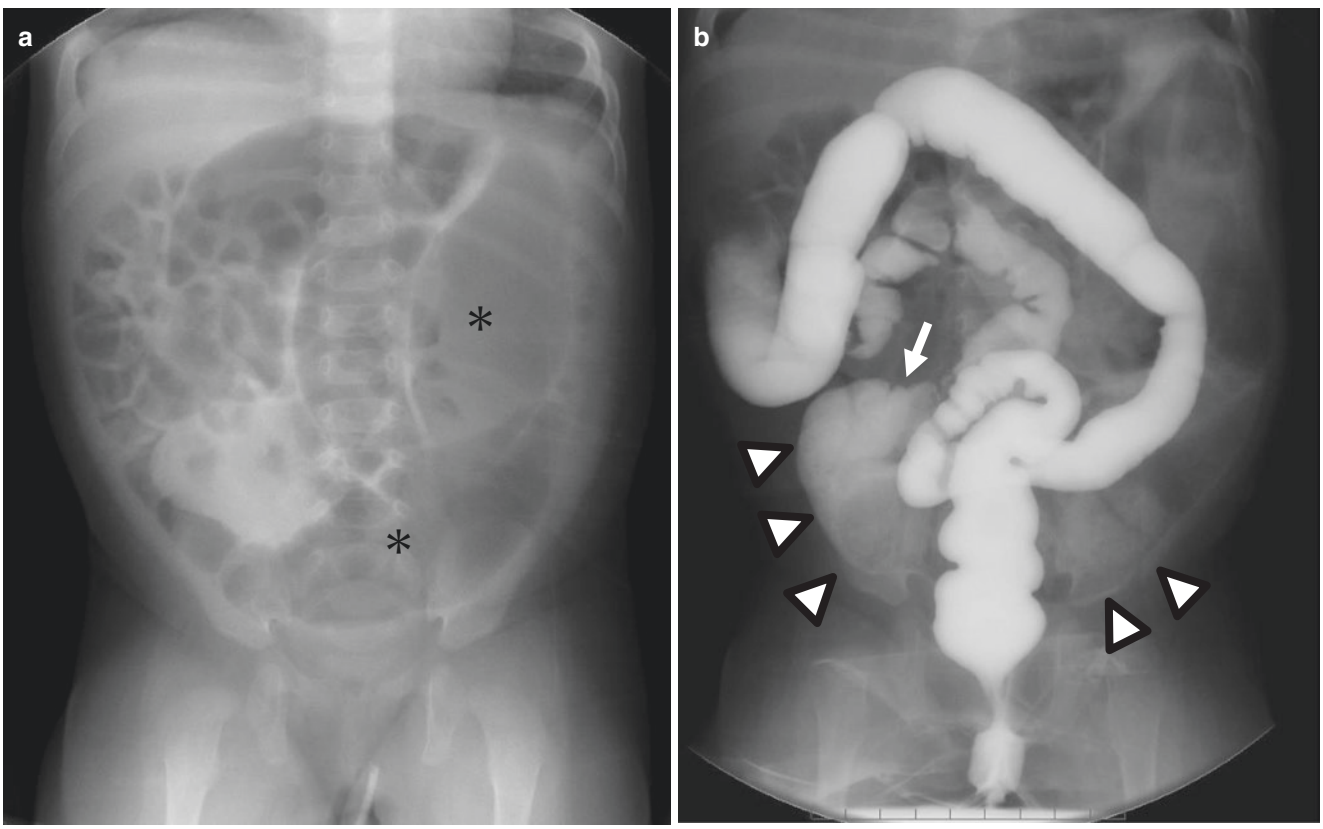

Fig. 11.6 (**a**, **b**) Total colonic aganglionosis in a 3-month-old girl. (**a**) Abdominal X-ray showing dilated intestine (*) as seen in short-type and rectosigmoid-type Hirschsprung's disease. (**b**) Contrast enema shows no dilatation of the colon but shows dilatation of small intestines (△). Caliber change is visible at the distal ileum (arrow), suggesting total colonic aganglionosis

11.2.3 Long Segment Aganglionosis

Figure 11.4a, b was taken from a patient with long-type Hirschsprung's disease on postnatal day 2 following delayed passage of the first meconium and a worsening abdominal distension. The X-ray shows the distended loops of the small bowel diffusely (*). Unlike in the previous figures, no dramatic changes can be seen in the colonic gases, and the contrast enema does not show a narrowing of the distal colorectum. The transverse colon shows dilatation, but the caliber change is unclear. After the examination, the patient passed a large quantity of stool.

Figure 11.5a, b shows the same patient when he was 25 days old. After the last examination, a drainage tube was inserted via the anus with the tip placed in the transverse colon. A drainage tube was left in place, and intraluminal irrigation was performed routinely. The abdominal distension improved greatly as a result, and an X-ray confirmed the disappearance of gas from the small bowel and the ascending to transverse colon. A contrast study showed a caliber change at the transverse colon (arrow) and dilatation of the proximal colon (△).

It is well known that narrowing of the distal colon might be unclear in long-type or total colonic aganglionosis, and patients with this condition are sometimes able to pass stool unassisted, both of which make a precise diagnosis more difficult [3]. As in this patient, the first examination in the early neonatal period may not show characteristic findings, and sometimes only repeated examination after drainage can give us clues necessary for a certain diagnosis. It is thus important to bear in mind that repeated examinations maybe necessary for patients with ambiguous initial findings [2].

11.2.4 Total Colonic Aganglionosis

Figure 11.6a, b shows a patient with total colonic aganglionosis at 3 months of age. She had vomiting early in life but was able to pass stool with the help of glycerin enemas. Due to the abnormal presence of gas on X-ray, the first contrast enema was performed when she was 3 months old. The X-ray showed a dilated intestine (*) as seen in short- and rectosigmoid-type Hirschsprung's disease. However, the contrast study revealed no dilatation of the colon but did show dilatation of the small intestine (△). A caliber change was seen at the distal ileum, suggesting total colonic aganglionosis. In cases such as this, it is sometimes difficult to determine the type of Hirschsprung's disease by X-ray or contrast enema.

The correlation between radiological detection of caliber change and the pathological transition zone is generally good [4] especially in the short and rectosigmoid types of Hirschsprung's disease [2]. However, in the long-type and total colonic aganglionosis, the aganglionic bowel may extend farther than the caliber change. Previous reports demonstrated a caliber change at the sigmoid colon, descending colon, splenic flexure, transverse colon, and hepatic flexure in total colonic aganglionosis [5, 6]. Repeated careful examination by a contrast enema may help achieve a definitive diagnosis. However, it is important to bear in mind that the aganglionic bowel may extend past caliber change and that intraoperative pathological diagnosis is crucial.

11.3 Motility Study

If radiological finding leads to the suspicion of Hirschsprung's disease, a motility study should be performed next. A motility study consists of anorectal manometry and colonic manometry. An anorectal manometry is used for patients with suspected Hirschsprung's disease to confirm the diagnosis. A colonic manometry is used in certain patients to assess the distribution of the intestines with normal and abnormal motility function.

11.3.1 Anorectal Manometry

11.3.1.1 Manometry of the Anal Canal

Manometry of the anal canal records the static pressure in the anal canal. It is important to identify the high-pressure zone with rhythmical changes in pressure in the anal canal, called rhythmic waves, which are caused by the autonomic contractions of the internal anal sphincter.

The resting pressure values are higher in term newborns than in preterm newborns and correlate with age [7]. The frequency of rhythmic waves is 10–15 times/min in normal controls, whereas patients with Hirschsprung's disease show a relatively lower frequency of about 8–10 times/min [8].

11.3.1.2 Rectoanal Inhibitory Reflex

When the wall of the rectum is distended by stool, the stimulation provided by the distention relaxes the internal anal sphincter. Pathways of this reflex remain to be completely elucidated. However, it is thought that stimulations received by sensory nerves in the rectal wall pass through the intrinsic nerve fibers or sacral nerve pathway and then relax the internal anal sphincter. Relaxation of pressure lasts for a few seconds and then gradually returns to the baseline with recovery of the rhythmic waves (Fig. 11.7a, c). This reflex, called the rectoanal inhibitory reflex, is mediated by the ganglion cells in the myenteric plexus. Patients with Hirschsprung's disease do not show this reflex due to the absence of ganglion cells in their myenteric plexus (Fig. 11.7b, d). In other words, the presence of the rectoanal reflex rules out Hirschsprung's disease.

The rectal suction biopsy remains the gold standard for the diagnosis of Hirschsprung's disease. However, it is invasive and can result in serious complications occurring in neonates [9, 10]. The contrast study is an effective screening test, and the rectoanal inhibitory reflex is an

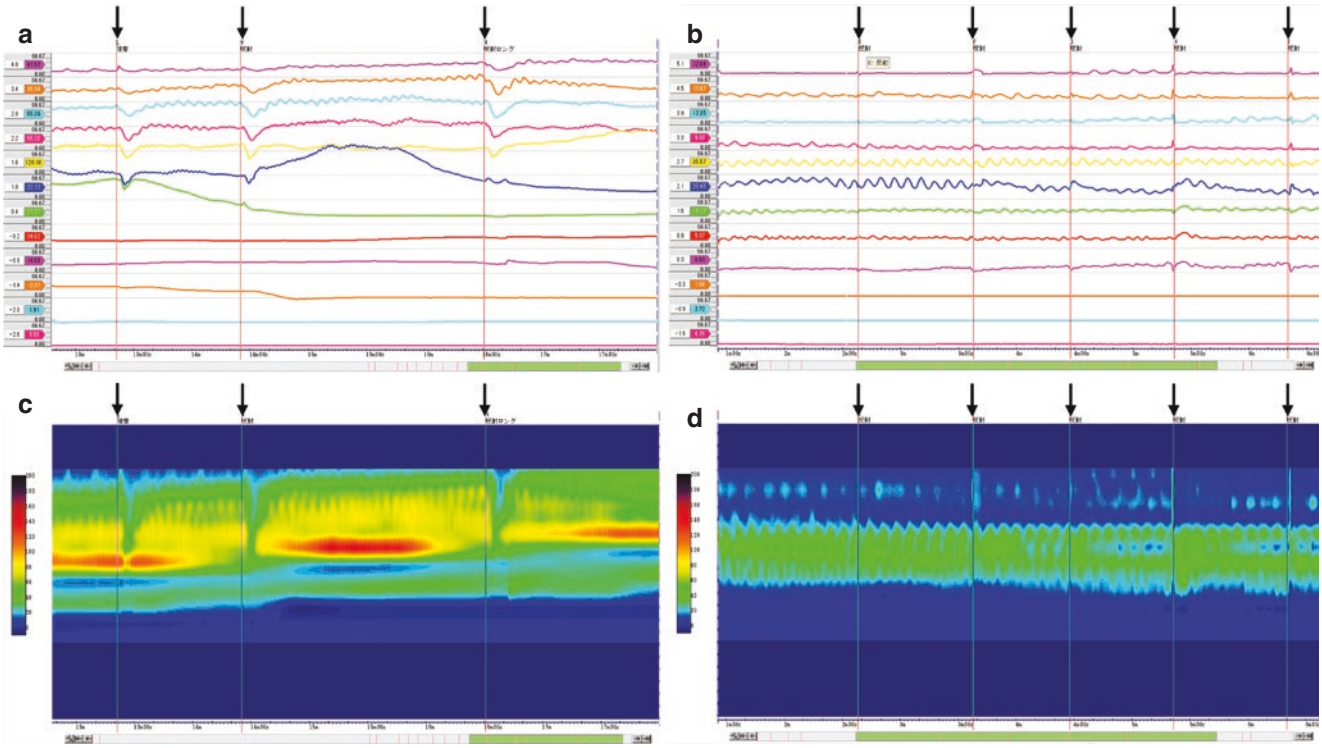

Fig. 11.7 (**a**–**d**) High-resolution anorectal manometry in normal control (**a**, **c**) and Hirschsprung's disease patients (**b**, **d**). (**a**) Balloon dilations (*arrows*) induced relaxation of basal pressure in the anal canal in normal controls. (**b**) No relaxation was seen in the anal canal of Hirschsprung's disease patients. (**c**, **d**) Same results as in **a** and **b**, respectively. Each pressure value is represented by a different color. Pressure changes in the anal canal were effectively visualized by different colors

excellent diagnostic criterion [8, 11–13]. The diagnostic accuracy of the rectoanal reflex is higher than that of the contrast enema [7, 14, 15]. In neonates and premature infants, normal rectoanal response is not obtained and may result in false negative [16, 17].

11.3.1.3 Methods for Anorectal Manometry

There are several different tools for performing anorectal manometry. Initially, balloon method [18] and infusion method using open tip catheter [19, 20] were mainly used, but water infused in the rectum sometimes affects the physiological reactions. Later, the semiconductor sensor [21] was introduced although the number of channels were not many and it was expensive. Recently introduced high-resolution manometry uses multichannel detectors to identify different locations simultaneously and visualize differences in pressure using various colors. This novel system for anorectal manometry is getting more popular in adults [22–25], and a couple of reports for diagnosing Hirschsprung disease in children were published recently [7, 26]. At our facility, we use the 12ch probe shown in Fig. 11.8. The distance between each sensor is 3.5 mm, allowing 4 cm of the anal canal and the rectum to be assessed simultaneously, rendering it unnecessary to adjust the depth of probe and shortening the time required for the procedure.

The examination requires about 30 min and little preparation. During the test, patients are sedated and placed in a supine position, while the physician places a small probe into the rectum. This probe is attached to a computer which measures how well the patient's rectal and sphincter muscles are working. After recording the resting pressure, a small balloon is inserted into the rectum, and the physician slowly inflates and deflates it to assess the rectoanal inhibitory reflex.

11.3.2 Colonic Manometry

Colonic manometry is used to assess the motility of the patient's colon by measuring colonic pressure or the strength of the muscle contractions within the colon. The final goal of treatment for Hirschsprung's disease is to achieve good intestinal motility needed for passing stools. To this end, surgeons may perform a pull-through procedure. Colonic manometry helps us to identify the distribution of the intestine with intact motility needed for this purpose.

The colonic manometry shown in Fig. 11.9 was performed for a 7-month-old girl who underwent an ileos-

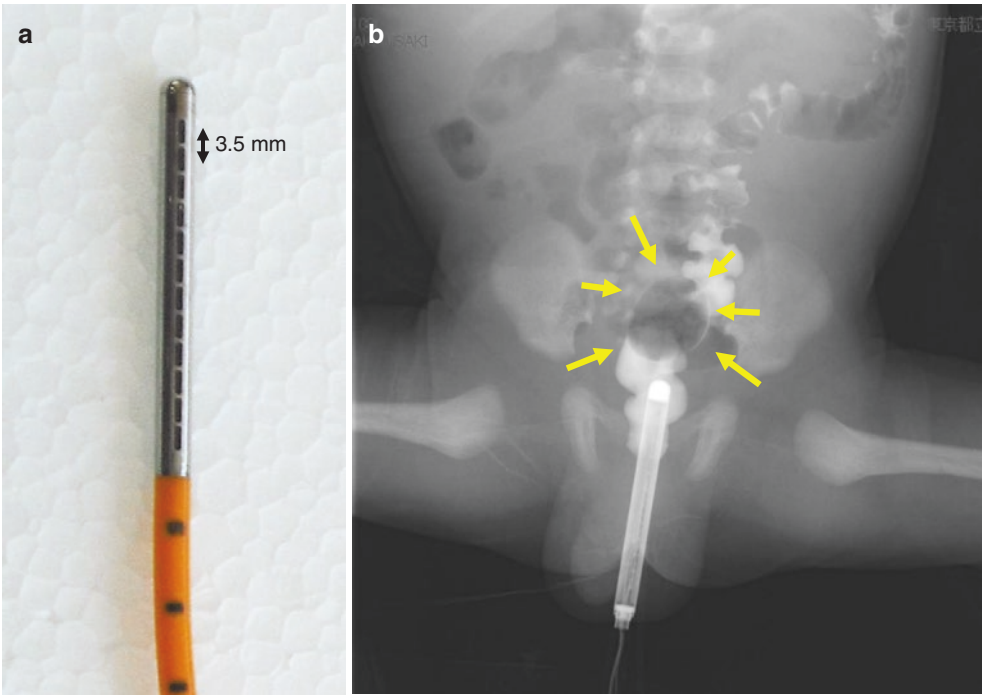

Fig. 11.8 (**a**, **b**) High-resolution manometry probe. (**a**) 12 channels were mounted at the tip of the probe. Distance between each probe was 3.5 mm. (**b**) The probe was placed in the anal canal. Note the inflated balloon in the rectum (arrow)

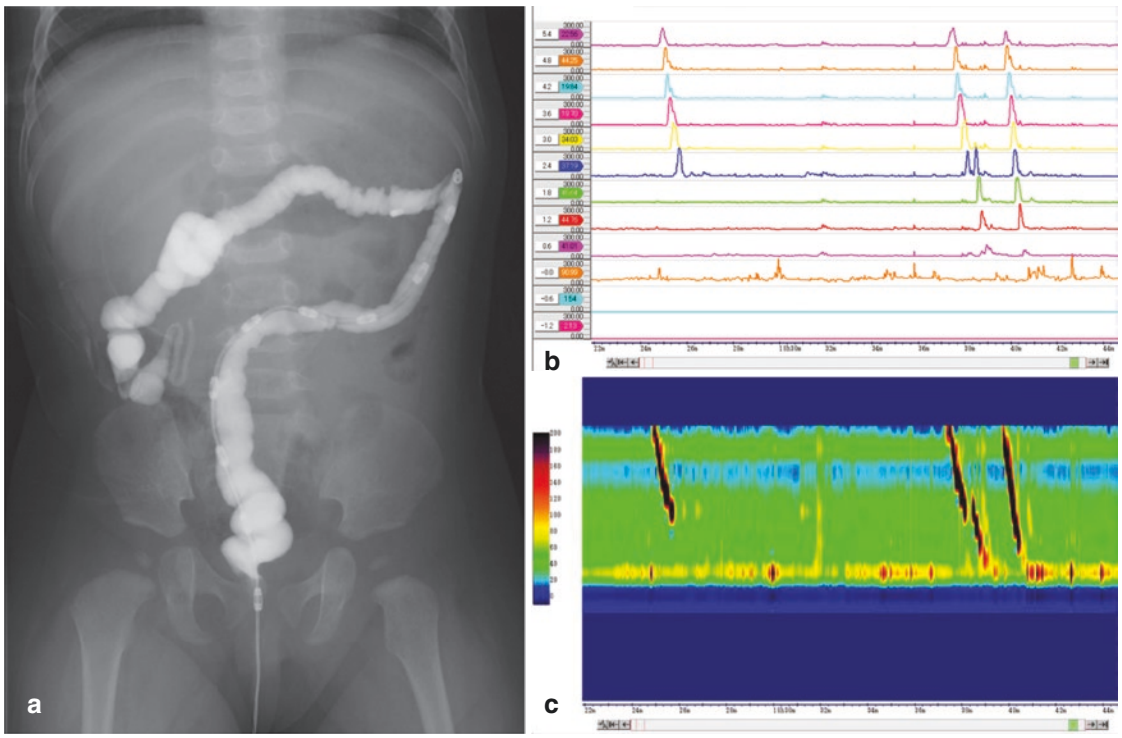

Fig. 11.9 (**a**–**c**) Colonic manometric study in a 7-month-old girl. (**a**) Motility catheter was inserted via her anus and placed within the distal colon. (**b**, **c**) Colon motility tracing demonstrated contractions propagating from transverse colon (top) to rectum (bottom), suggesting normal colonic motility

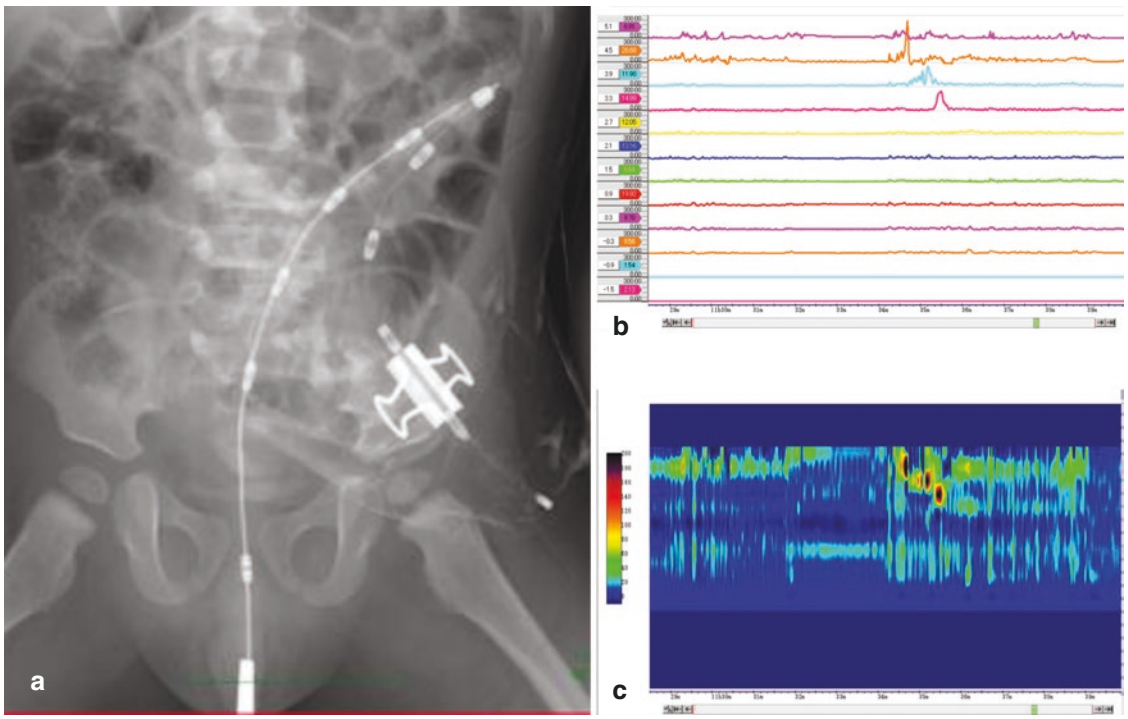

Fig. 11.10 (**a**–**c**) Colonic manometric study in a 1-year-old boy with transverse colostomy. (**a**) Motility catheter was inserted via his anus into the stoma. (**b**, **c**) Colonic motility tracing showed contractions propagating at three consecutive points from the stoma to splenic flexure, suggesting a segment of the intestine with normal motility distal to the stoma

tomy in the neonatal period after receiving a preliminary diagnosis of total colonic aganglionosis. A motility catheter was inserted via the anus and placed within the distal colon. Colonic motility tracing demonstrated contractions propagating from the transverse colon (top) to the rectum (bottom), suggesting normal colonic motility and a much lower likelihood of Hirschsprung's disease. She then underwent surgery for anastomosis of the proximal and distal bowel and was able to pass stool through the anus normally.

The test shown in Fig. 11.10 was performed for a 1-year-old boy who underwent a transverse colostomy due to intestinal perforation. The anorectal manometry and rectal suction biopsy findings were compatible with Hirschsprung's disease. A motility catheter was inserted via his anus and reached the stoma. Colonic motility tracing showed contractions propagating at three consecutive points from the stoma to the splenic flexure, suggesting a segment of the intestine with normal motility distal to the stoma. The patient underwent surgery to create a new stoma 11 cm distal from the first stoma and then underwent pull-through surgery 2 months later. His postoperative control of defecation was good.

11.4 Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) is a novel technology that allows real-time in vivo characterization of architectural and cellular details during an endoscopy. In gastroenterology, this new device is effective for diagnosing malignant tumors [27, 28] and inflammatory bowel diseases [29]. CLE is able to visualize with fluorescein at 1000-fold magnification at a certain focus depth and appropriate wavelength excitation.

Recently, our group evaluated the human enteric nervous system (ENS) networks in patients with an intact enteric nervous system using CLE and achieved detailed visualization within the small intestine and large colon [30]. CLE clearly visualized ladder-like structures with negatively identified nuclei inside resembling the myenteric plexus (Fig. 11.11). In surgical interventions for Hirschsprung's disease, an intraoperative pathological diagnosis is mandatory to assess the extent of aganglionosis. To assess the distribution of ENS, an easy, quick, and accurate method is ideal. CLE can visualize the interior of the gut sequentially by moving the probe from one location to another continuously. This continuous visualization is a significant advantage compared to intraoperative pathological diagnosis. In

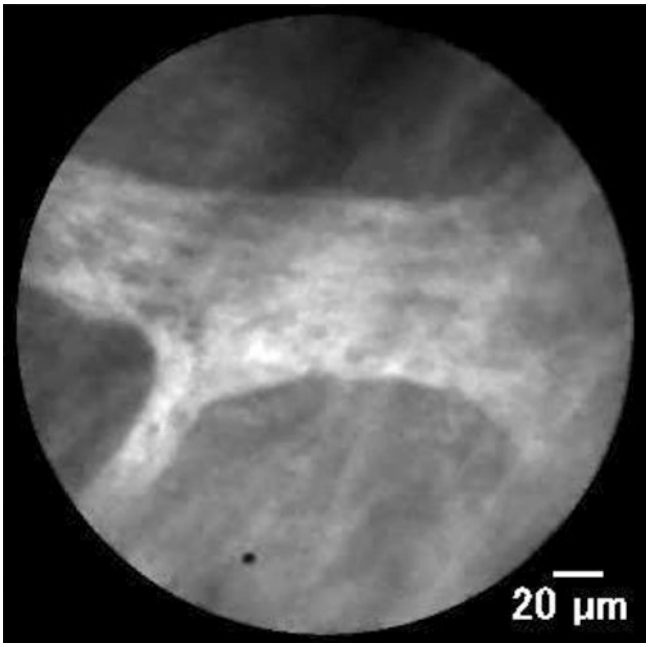

Fig. 11.11 Confocal laser endomicroscopy (CLE) clearly visualized a ladder-like structure with negatively identified nuclei inside resembling myenteric plexus

the near future, CLE may become a novel tool for visualizing the human ENS, revolutionize the way we diagnose Hirschsprung's disease, and prove to be a better alternative to intraoperative histopathological diagnosis.

11.5 Conclusion

The most important diagnostic tools for Hirschsprung's disease are histopathological and immunohistochemical evaluations of suction and full-thickness biopsies. However, clinical symptoms, radiological diagnosis, and manometric studies should be taken into account to achieve a better understanding of the disease in each patient. To improve surgical interventions, preoperative prediction of the location of the transition zone through radiological diagnosis and manometric studies and confirmation of the existence of an intact enteric nervous system in the residual bowel by intraoperative pathological diagnosis or scanning by CLE are crucial.

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Rectal Biopsy

12

Koichiro Yoshimaru

Abbreviations

AChE	Acetylcholinesterase
HD	Hirschsprung's disease
HE	Hematoxylin and eosin
IND-B	Intestinal neuronal dysplasia type B
RMB	Rectal mucosal biopsy
RPB	Rectal punch biopsy
RSB	Rectal suction biopsy

12.1 Introduction: History of Rectal Biopsy

A histopathological examination is mandatory for the diagnosis of Hirschsprung's disease (HD), which occurs due to the absence of enteric ganglion cells [1]. Usually, ganglion cells are completely absent in the narrow colonic segment of the HD patient, and the aganglionic narrowed segment visually always includes the rectum [2]. Thus, the biopsy of the distal rectum of patients suspected of having HD could reveal the presence or absence of ganglion cells [2]. This histopathological finding made rectal biopsy procedure as an important diagnostic investigation along with clinical symptoms, X-ray, contrast enema, and anal pressure examination.

The history of rectal biopsy is shown in Table 12.1. Open wedge full-thickness biopsy (FTB) with Auerbach's myenteric plexus was initially described by Swenson et al. [3]; however, this method requires general anesthesia and is invasive and associated with complications including complicated bleeding, infection, and/or scarring. In 1960, the discovery, which the submucosal ganglion cells in the rectum presented at the same level as the myenteric plexus [4], widened the possibility for the diagnosis of HD performing rectal mucosal biopsy (RMB) as the lesser invasive technique. At that time, the basic histopathological analysis was taken by hematoxylin and eosin (HE) staining; however, RMB with HE staining had a disadvantage for the accurate diagnosis. This is because it was very difficult even for the experienced pathologists to diagnose HD by the negative finding as an absence of submucosal ganglion cells in tiny size of specimen [9]. In this era, Meier-Ruge demonstrated acetylcholinesterase (AChE) staining using frozen section in 1968 and 1972 [7, 8], which exhibits the definitive positive findings such as AChE-positive nerve fibers in the lamina propria and hypertrophic nerve bundles in the submucosal layer in HD. These findings were clearly visualized even in tiny submucosal specimen, which improved the diagnostic accuracy using RMB specimen. On the other hand, the usage of frozen section has not been the universal procedure. Currently, a global analysis including 30 countries demonstrated that 85.1% of pediatric surgeons use rectal suction biopsy (RSB) as RMB, whereas 14.9% of them prefer FTB under general anesthesia [10], and the European Paediatric Surgeons' Association showed that rectal biopsies are obtained using the RSB by 61% respondents and via open FTB by the other 39% respondents [11]. Taken together, FTB with HE staining; RMB with HE staining and immu-

Table 12.1 The dawn of the histopathological analysis of Hirschsprung's disease

Year	Author	Events	References
1959	Swenson	Open full-thickness biopsy	[3]
1960	Gherardi	The discovery of the same level of M-P and A-P	[4]
1961	Shandling	Rectal punch biopsy	[5]
1965	Dobbins	Rectal suction biopsy	[2]
1969	Noblett	Rectal suction biopsy, refined	[6]
1968	Meier-Ruge W	AChE staining for rectal mucosal biopsy	[7]
1972	Meier-Ruge W	AChE staining for rectal mucosal biopsy	[8]

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nostaining such as calretinin, S-100, and so on; and RMB with AChE staining are currently selected based on each institutional facility and preference.

12.2 Anatomy for Apropriate Sampling

The representative histopathological findings of appropriate tissues are shown in Fig. 12.1. In the specimen of normal study, ganglion cells are presented both in acetylcholinesterase (AChE) histochemistry (Fig. 12.1a) and hematoxylin and eosin (HE) staining (Fig. 12.1c). In the specimen of HD, AChE-positive nerve fiber in the lamina propria and hypertrophic nerve bundle in the submucosal layer are presented without ganglion cells (Fig. 12.1b); structurally well-defined wavy-shaped hypertrophic nerve bundles in the submucosal layer are presented without ganglion cells (Fig. 12.1d). In contrast, an "inappropriate" sample is shown in Fig. 12.2, which consists with the sample without submucosal layer (Fig. 12.2a, c) and the sample covered with squamous layer (Fig. 12.2b, d). The appropriate sample includes the enough amount of submucosa measuring at least 3 mm in diameter with at least one-third of its thickness in order to contain the submucosal layer [12–14] and is not covered by the squamous layer, indicating that the biopsy site is a physiological hypoganglionic zone near the dentate line. To avoid performing an inadequate RMB, the precise understanding of the rectal anatomy is essential.

The anatomical interrelationship of the dentate line, the internal sphincter muscle, and the external sphincter muscle and the distribution of Auerbach's and Meissner's plexus are shown in Fig. 12.3. The dentate line can be seen as a border line between the columnar epithelium and the stratified squamous epithelium. The distribution of enteric plexus

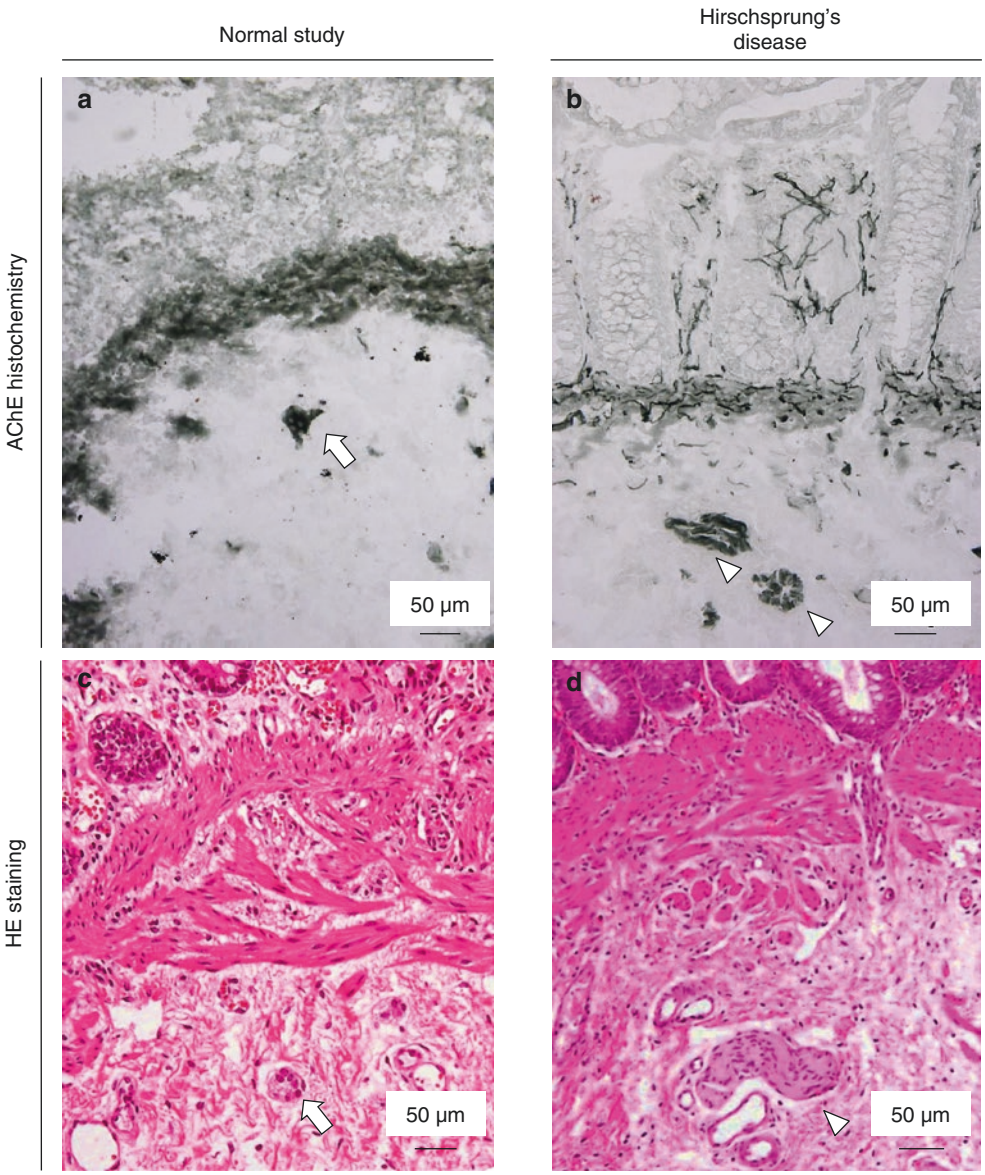

Fig. 12.1 The representative findings of normal study and Hirschsprung's disease tissue sample. The ganglion cells in Meissner's plexus are presented at the submucosal layer in normal study (white arrow) (**a**, **c**); The AChE-positive nerve fibers at the lamina propria and hypertrophic nerve bundles (white arrow head) without ganglion cells at the submucosal layer are identified in Hirschsprung's disease (**b**, **d**). (**a**) and (**b**) are stained with acetylcholinesterase histochemistry; (**c**) and (**d**) are stained with hematoxylin and eosin

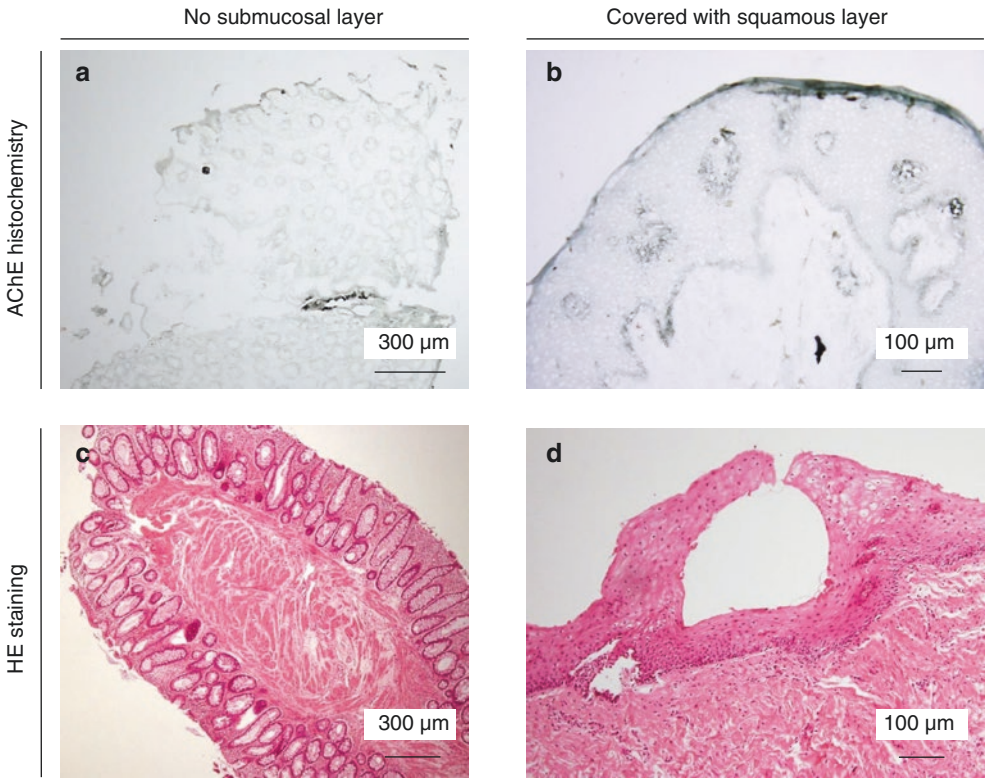

Fig. 12.2 The representative findings of the inappropriate tissue samples. The specimens without the submucosal layer and covered with squamous layer are defined as "inappropriate" sample. (**a**) and (**b**) are stained with acetylcholinesterase histochemistry; (**c**) and (**d**) are stained with hematoxylin and eosin

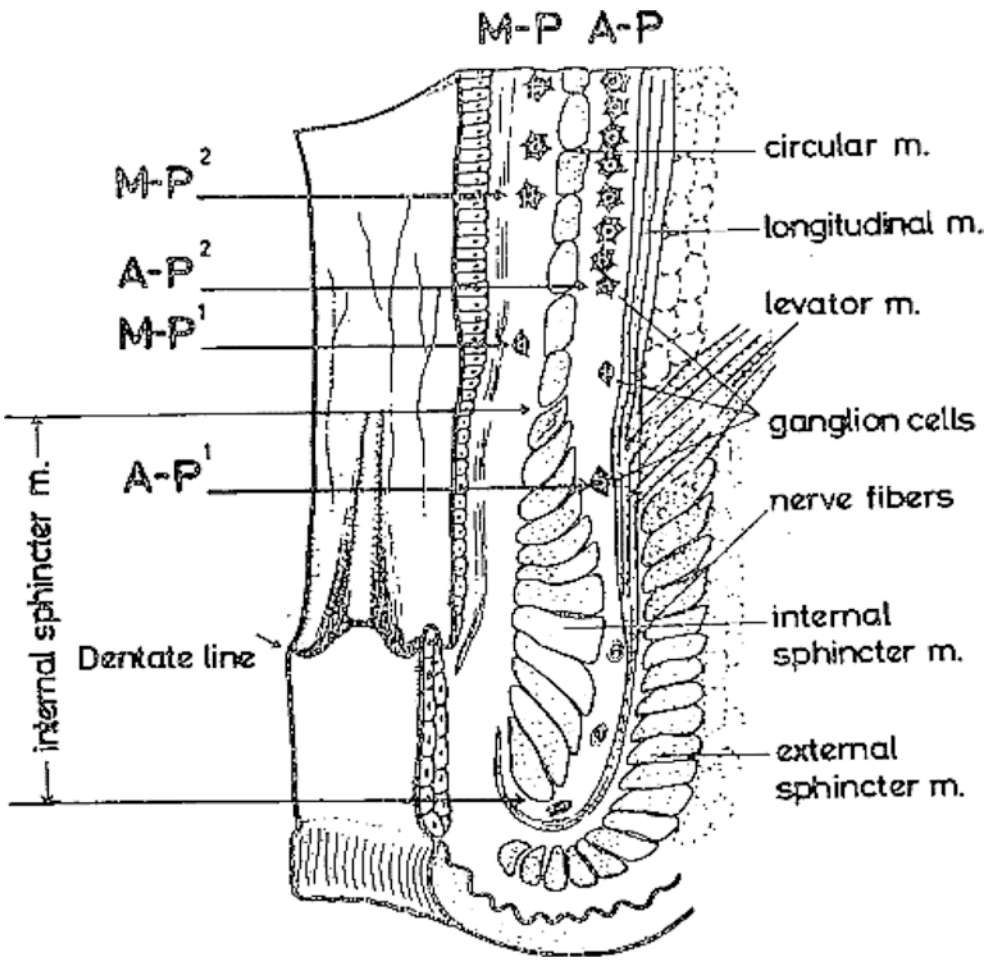

Fig. 12.3 The schematic image of the rectum and anus. The distribution of ganglion cells and nerve fibers and the location of dentate line, internal sphincter muscle, and external sphincter muscle are shown. A-P^1 and M-P^1 indicate the terminal distribution of Auerbach's plexus and Meissner plexus. A-P^2 and M-P^2 indicate the terminal distribution of "normal" Auerbach's plexus and Meissner's plexus. The area between P^1 and P^2 indicates the "physiological hypoganglionic zone." *m* muscle, *M-P* Meissner's plexus, *A-P* Auerbach's plexus. This figure is reprinted with permission from *Journal of Japanese Society of Pediatric Surgeon*

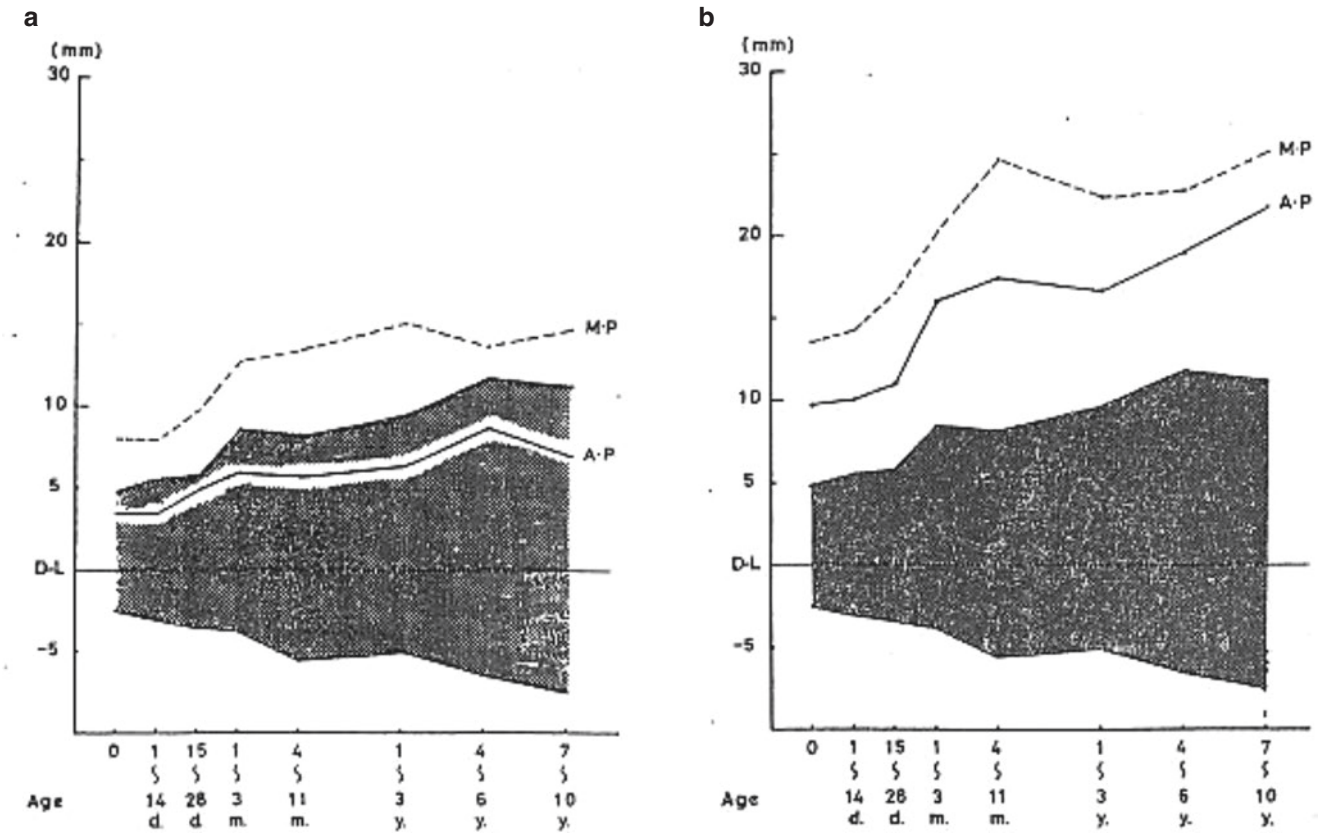

Fig. 12.4 The distance of the terminal innervation of Meissner's and Auerbach's plexus above the dental line according to the patient's age. (**a**) Shows the terminal innervation, and (**b**) shows the terminal normal innervation. Dot line shows the terminal innervation of Meissner's plexus; solid line shows the terminal innervation of Auerbach's plexus; brown window shows the window of the internal sphincter muscle. *M-P* Meissner's plexus, *A-P* Auerbach's plexus, *D-L* dentate line, *d* days old, *m* moths old, *y* years old. This figure is reprinted with permission from *Journal of Japanese Society of Pediatric Surgeon*

gradually which sifting from normoganglia to oligoganglia is found according to the location from oral side to anal side. The physiological hypoganglionic zone is therefore generally presented at the end of the rectum. Moreover, the level of the end of the innervation of Auerbach's and Meissner's plexus is different, and the end of Meissner's plexus is presented more at the oral side than the end of Auerbach's plexus. In addition, the level of the end of the innervation is altered in accordance with aging, showing in Fig. 12.4. The end of innervation including the oligoganglia of Auerbach is distributed into the area of the internal sphincter muscle, but not in Meissner's plexus (Fig. 12.4a). Concerning the end of normal innervation of Meissner's plexus which is important for the adequate biopsy sampling, it is located above 5–10 mm from the border of internal sphincter muscle and is altered according to the patient's age (Fig. 12.4b) [15].

Based on the rectal anatomy, biopsies were carried out at an appropriate distance above the dental line according to the patient's age (1.5 cm, <1 month old; 2.0 cm, <1 year old; 2.5 cm, <3 years old; 3.0 cm, >3 years old in Meissner's plexus; 2.0 cm, <1 month old; 2.5 cm, <1 year old; 3.0 cm, <3 years old; 3.5 cm, >3 years old in Auerbach's plexus) in order to avoid confusion with physiological zones of hypoganglionosis (Table 12.2) [15–17].

Table 12.2 The distance from the dentate line according to age

	Distance from dentate line	
Age	A-P	M-P
<1 month	1.5 cm	2.0 cm
<1 year	2.0 cm	2.5 cm
<3 years	2.5 cm	3.0 cm
≥3 years	3.0 cm	3.5 cm

A-P Auerbach's plexus, *M-P* Meissner's plexus

12.3 Techniques of Full-Thickness Biopsy (RTB)

Patients especially at neonatal and infantile periods are usually receive general anesthesia and are placed at the lithotomy position. To retract the round area of the biopsy site, traction suture is initially performed at the back side (#1) and

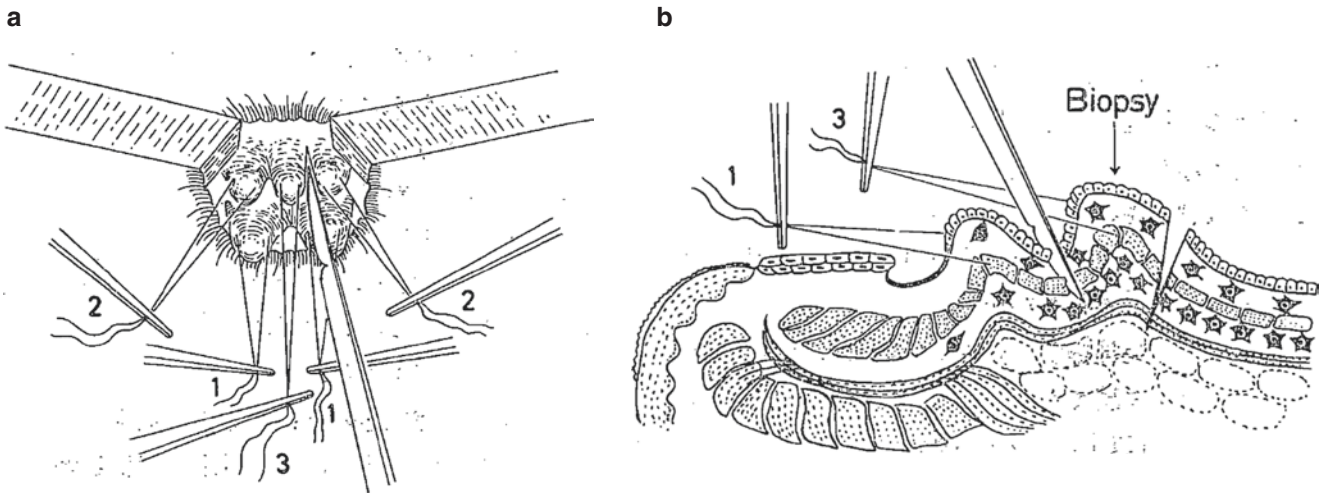

Fig. 12.5 Full-thickness biopsy. (**a**) To retract the round area of the biopsy site, traction suture is initially performed at the back side (#1) and the lateral side (#2). (**b**) The biopsy is performed using a knife. This figure is reprinted with permission from *Journal of Japanese Society of Pediatric Surgeon*

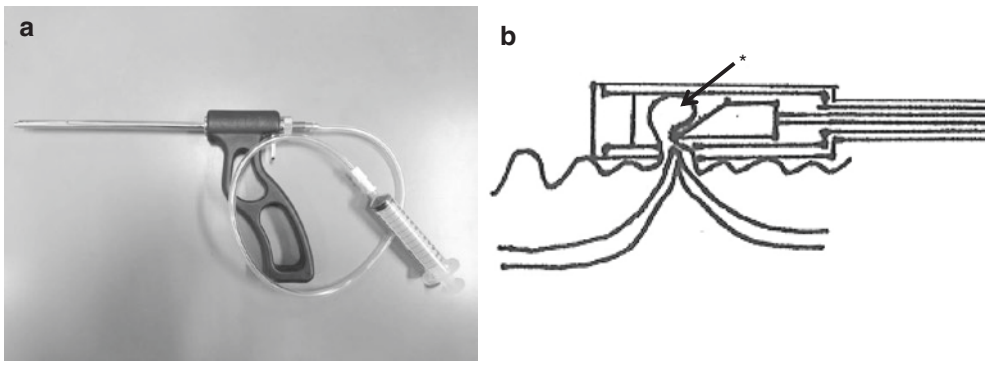

Fig. 12.6 Suction biopsy. (**a**) The representative instrument when performing the suction biopsy (rbi2, Suction Rectal Biopsy System, manufactured in Australia, Aus Systems Pty Ltd., Australia). (**b**) The schematic image of technique of the suction biopsy. Asterisk indicates the obtaining sample

the lateral side (#2), which is located at the 1–2 cm oral side of the dentate line. Following this traction suture, the biopsy is done by suturing thread #3 (Fig. 12.5a). To include both of the internal and external muscle layer for the evaluation of both Meissner's and Auerbach's plexus, the sample size of 0.5 × 1.0 cm is recommended (Fig. 12.5b). Following the confirmation of the complete hemostasis, suturing biopsy site closure is performed.

12.4 Techniques of Rectal Suction Biopsy (RSB)

Regarding the RMB methods, suction biopsy was first described by Dobbins et al. [2] and refined by Noblett [6]. Numerous techniques and devices have been established. Currently, five different types of RSB instruments were reported, the most common ones being rbi2 (Aus Systems, Australia) (65.0%) (Fig. 12.6a), Solo-RBT (SAMO Biomedica, Bologna, Italy) (15.0%), and multipurpose suction biopsy kit (Quinton Instrument Company, Seattle, USA) (8.3%), followed by SBT-100 (Medical Measurements Inc., Hackensack, USA) (6.7%) and various self-made devices (5.0%) [10]. The standard procedure of RSB is introduced by Muise et al. [18] as follows, and the representative RSB instrument and schematic procedure are shown in Fig. 12.6b: Patients are placed at the lithotomy position followed by the insertion of the lubricated biopsy instrument along the posterior wall of the rectum; position the opening for the cutting blade 2 cm above the dental line, and aim the blade posteriorly, apply suction, and trigger the cutting blade to obtain tissue specimen. Different instrumentation sets recommended different amounts of suction pressure be applied to obtain an appropriate sample. The rbi2 (Aus Systems, Australia) recommends calibration to 300 mm H_2O prior to use and then withdrawing the plunger to 3–5 ml (using 10 ml syringe), or ideally 150 cm H_2O when using manometer [19]. A median of two (range, 1–5) specimens is routinely taken [10]. In RSB, mechanical biopsy devices may have the advantage of reproducibly obtaining a standard volume of tissue sample.

12.5 Techniques of Rectal Punch Biopsy (RPB)

As the other option of RMB, punch biopsy technique was first described by Shandling [20]. As the representative technique of punch biopsy, the method of "K-PUNCH," which is our original technique, is introduced as follows [21]: Briefly, (1) an S-moid forceps (Nishihata) (No. 15602; Nagashima Medical Instruments Co., Ltd., Tokyo, Japan) and a non-specific blood-collecting tube with a 6-mm hole drilled at the top of the tube are prepared prior to the biopsy procedure (Fig. 12.7a). (2) Patients are fixed in the lithotomy position. (3) A non-specific blood-collecting tube with a 6-mm hole drilled into the top of the tube is gently inserted to the rectum (Fig. 12.7b, c). (4) Appropriate lateral pressure is applied in order to fix the side aperture securely against the mucosal surface. The protrusion of the rectal mucosa into the internal cavity is then clearly observed with the full view of the operator under a pen light (Fig. 12.7d). With regard to the tube, a non-specific blood-collecting tube is generally used; however, a 1.5-ml micro tube is occasionally used for neonates, and a 15-ml centrifuge tube is occasionally used for older children depending on the size of the rectum (Fig. 12.7f). Following the identification of the appropriate biopsy site by two abovemen-

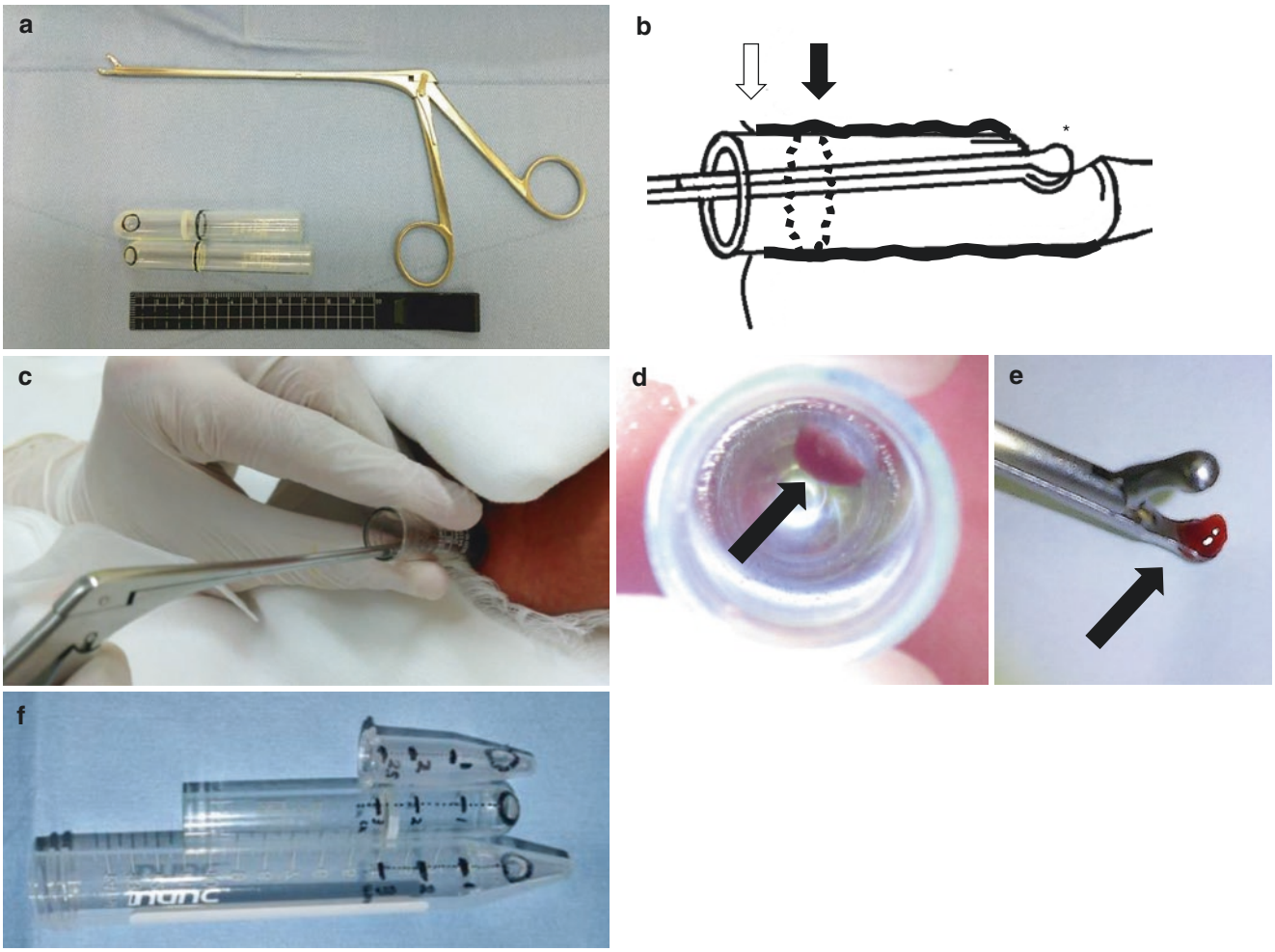

Fig. 12.7 The detailed technique of "K-PUNCH" biopsy. An S-moid forceps (Nishihata) and a handmade rectal biopsy tube with a 3-mm hole drilled at the top of tube. The tube is marked at 3 cm from the drilled hole (**a**). A schematic drawing representing the insertion of the tube into the rectum from the lateral view. The insertion of the tube causes the rectal mucosa to protrude. The rectal mucosa is then grasped by the forceps (indicated by the asterisk). The white arrow indicates the anal verge; the black arrow indicates the dental line (**b**). The external appearance during the "K-PUNCH" biopsy procedure. The tube is fixed by the left hand to stabilize the operator's view (**c**). The internal view during the "K-PUNCH" biopsy procedure. A full, clear view of the operative field is achieved. The black arrow indicates the protruding rectal mucosa (**d**). A specimen of appropriate size was harvested. The black arrow indicates the specimen (**e**). Three types of tube are ordinarily used in accordance with the patient's side. The tube in the upper position is a 15-ml centrifuge tube, the tube in the middle is a non-specific vessel tube, and that in the lower position is 1.5-ml micro tube. The diameters of all of the tubes are written on the lateral part of the tube in order to measure the distance from the dental line during biopsy (**f**). This figure is reprinted with permission from *Pediatric Surgery International*

tioned methods, the mucosa is completely grasped with the abovementioned laryngeal S-moid forceps, and the specimens are pulled off with the resistance disappearing at up to 1–2 s (Fig. 12.7e). If the specimen could not be obtained with the abovementioned resistance, the grasped specimen was released in order to avoid massive bleeding and unnecessary deep-layer biopsy. In contrast, when the specimen could be obtained without any resistance, this indicated that the harvested specimen is too shallow to be adequate. This principle is commonly applied, regardless of the age of the patients.

Appropriate resistance modulated by the operator while grasping the tissue is most important for obtaining an appropriate specimen. Two or three additional biopsies are immediately performed at other portions of the rectum wall, while the concurrent turning of the biopsy tube contributed to the compressive hemostasis of biopsy site.

12.6 Complications of Rectal Biopsy

The numerous reports on the complications associated with rectal biopsy such as the inappropriate sampling, prolonged bleeding (requiring transfusion, repacking, and/or cautery), perforation, infection, and abscess formation have been described [5, 22–34]. However, the complications are nowadays rare, which is known to be 6.6% of patients in FTB [35] and be up to 2% of patients in RMB (regardless of the type) [18, 36] thanks to the various refinements and the practician's carefulness. In the procedure of RSB, if the suction is applied with too high pressure, it will lead to extracting the unexpected larger specimen often including the muscle layer, resulting in the prolonged bleeding and the perforation. On the other hand, the incidence of the inappropriate tissue sampling due to the insufficient negative pressure application is 8–26%, resulting in repeat biopsy to definitive diagnosis [28–30, 33, 37]. To obtain the appropriate sample without any complications, the adequate negative pressure application is important. In the procedure of RPB, 3.9% of the inappropriate tissue sampling and 0.1% of the severe complications were obtained based on the Japanese study [9, 21, 38, 39]. The study by Alizai et al. [28] noted 102 rectal mucosal punch biopsies with no major complications such as bleeding requiring blood transfusion, intestinal perforation and sepsis, and 4% of inappropriate sample rates.

12.7 Indication for Performing Rectal Biopsy to Neonates and Premature Infants

A Japanese nationwide survey revealed 38.8–53.4% of HD patients were diagnosed in the neonatal period [40], and Yoshimaru et al. showed the 44.5% of neonates who underwent RMB which were diagnosed with HD [21]. These large population studies concluded the importance of rectal biopsy in the neonatal period. Concerning the premature infants, HD is known to be rare. Systematic review demonstrated by Duess et al. [41] showed a prevalence rate of 6% of preterm infants diagnosed with HD. Not only the fact that there does not seem to be a substantial difference between preterm and full-term infants with HD as regards the presence of obstructive signs and symptoms only but also that higher prevalence of HD in recent years has been reported in premature infants compared to previous years recommends us taking a careful consideration for the presence of HD in premature infants, resulting in the reduction of the risk of HD-associated enterocolitis, which can progress to life-threatening conditions such as severe dehydration, shock, and sepsis [40]. On the other hand, the complications of RMB such as rectal bleeding, bowel perforation, and sepsis were significantly more frequent in newborns and infants compared to older children [36]. As the other remark, the low sensitivity for diagnosing HD in this age range should be noted. Meinds et al. demonstrated that a patient's age influenced the accuracy of RMB for diagnosing HD and the sensitivity of RMB outcomes was significantly lower when the RMB was obtained in patients younger than 39 days [42]; this is because immaturity of enteric nervous system in this age range is dynamically developing and therefore quickly changing even after birth [9]. This result indicated that repeated RMB in infant may occasionally be required. Taken together, careful RMB should be done in this period because RMB for neonates and premature infants is necessary but has a higher risk.

12.8 Indication for Performing Rectal Biopsy to Elder Children and Adults

It is generally accepted that RMB in elder children and adults does not yield adequate tissue specimens for the pathological analysis. A possible reason for this is the difficulty in obtaining an accurate biopsy specimen due to the age of the patient because morphological changes, such as an increase in the thickness of the rectal wall, mucosal edema, and fibrous tissue, may occur in older patients who receive chronic enemas and who subsequently develop edema of the mucosal layer [12, 18, 43]. Furthermore, the longer distance of the normal hypoganglionic or aganglionic segment from the dental line in older children and adults—which gradually increased from 1.0 cm in the neonatal period to approximately 3.5 cm in older children and adults—may have an impact on the difficulty of biopsy in children and adult groups [15, 21]. Thus, RMB is considered to be difficult in older children and

adults, and the proposal of rectal biopsy in patients within this age range remains controversial and a challenging problem at present [18].

From the 1990s, the indication for RMB was expanded to include the diagnosis of intestinal neuronal dysplasia type B (IND-B) in the allied disorders of Hirschsprung's disease [44]. IND-B is known to occur in adulthood as well as childhood [43]; thus, safe biopsy techniques are necessary to accurately diagnose IND-B in pediatric and adult patients with chronic constipation.

Some reports, moreover, have described children and adult patients including 67-year-old women with chronic constipation being diagnosed with HD [45–48]. Acute intestinal obstruction, perforation, and volvulus sometimes overlap with HD in children and adults [49–51]. Yoshimaru et al. demonstrated that 33 children and 4 adults were diagnosed with HD [21]. IND-B should also be taken into account because it is a possibility in children who suffer from chronic constipation [43]. These previous reports indicate that rectal biopsy in this age range has an important role for the undelayed diagnosis of HD and IND-B.

12.9 Conclusions

In this chapter, the introduction of the history, the anatomy, and the indication of the rectal biopsy are conducted. The most important factor performing a biopsy is obtaining an enough size of samples with an adequate and consistent level regardless of the type of procedure [10]. The biopsy techniques have been refined, resulting in the reduction of the rate of complications. Although most bleedings following rectal biopsy are self-limited and not concerning, therefore, the episode of perforation and sepsis is rare; the practician must be aware of the possibility of the complications.

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Enterocolitis

13

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13.1 Introduction

The most common complication of Hirschsprung's disease (HSCR) is Hirschsprung's disease-associated enterocolitis (HAEC) [1]. HAEC manifests the clinical symptoms of bacterial enterocolitis with fecal stasis, including abdominal distention due to progressive bowel distention, diarrhea, foul-smelling stool, and fever. HAEC sometimes becomes a serious and life-threatening condition, such as sepsis and shock. Historically, two infants who died from an HAEC-like condition were first described by Professor Harald Hirschsprung to the Congress in 1886 [2]. The association between HSCR and HAEC was recognized by Swenson and Fisher in 1956 [3], and this process was later described in detail by Bill in 1962 [3–5]. In the past 60 years, there have been major advances in surgical procedures, such as Swenson, Duhamel, original Soave, Z-shaped anastomosis, and transanal endorectal pull-through (TAEPT). However, HAEC still has frequent complications before and after surgery, and the pathogenesis of HAEC has not been completely resolved [1].

The morbidity of HAEC is reported to range from 6% to 60% prior to definitive pull-through surgery and from 5% to 42% after surgery. The incidence of HAEC is similar in the preoperative and postoperative stages. The incidence of HAEC widely varies because of the different diagnostic criteria [1, 4, 6–13]. Several features appear to be associated with an increased risk of HAEC. HAEC preoperatively occurs more frequently in patients with the long-segment type and with Down syndrome [14–16]. Postoperative risk factors of the occurrence of HAEC include retained aganglionosis of the distal rectum, dysmotility following pull-through surgery, anastomotic stricture, and muscular cuff stenosis following the Soave procedure [8].

Generally, HSCR has a relatively favorable outcome after pull-through surgery. The mortality of HAEC has been reported to range from 1% to 10% caused from sepsis and shock in neonates without early diagnosis and effective treatment prior to definitive surgery [4, 7]. Prato et al. [7] demonstrated that Down syndrome, preoperative enterocolitis, and the length of aganglionosis are principal risk factors in an unfavorable outcome. They showed that overall death among 945 cases of HSCR occurred in 32 (3.4%) patients by reviewing the literature, and they examined long-term outcome and causes of mortality since the early 1990s. Causes of death included congenital heart failure in 34% of patients, HAEC in 31%, intestinal failure caused by extensive small bowel involvement by aganglionosis in 12%, and others.

Recently, Taguchi et al. [1] reported the current status of HSCR in Japan based on a retrospective, nationwide survey for four decades as follows: between 1978 and 1982, between 1988 and 1992, between 1998 and 2002, and between 2008 and 2012. The incidence of preoperative enterocolitis was 17.2% between 2008 and 2012, and this rate was markedly decreased compared with 29.2% between 1978 and 1982. The rate of mortality of preoperative enterocolitis was obviously decreased to 0.3% between 2008 and 2012 versus 6.5% between 1978 and 1982. Over the last decade, there has been remarkable improvement in the mortality rate associated with the small intestine (aganglionosis extending orally to greater than 30 cm of the terminal ileum). Management strategies for HAEC have been developed that can be applied before and after definitive pull-through surgery. These strategies include prompt application of preventive strategies for HAEC, parenteral and enteral nutrition, and probiotics, which might have contributed to the decreased mortality rate [1, 17]. In this chapter, we review the pathogenesis, diagnosis, therapeutic management, and prevention of HAEC.

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13.2 Pathogenesis

13.2.1 Distal Aganglionosis

Historically, distal obstruction due to aganglionosis has been considered as the sole causative factor in the development of HAEC [3, 18]. Functional obstruction in the distal colon can lead to fecal stasis and then overproduction of pathogens, mainly bacteria. Consequently, mucosal invasion of bacteria causes systematic inflammation, which is called bacterial translocation. In an experimental study, Caniano et al. [19] used the piebald-lethal murine model and found that obstruction of the distal colon resulted in a loss of mucosal barrier integrity. This loss allowed intraluminal pathogens to move through the mucosal surface and enter the circulation. However, other possible etiologies have been considered because occurrence of HAEC has been observed prior to surgery, as well as after pull-through surgery [11–13].

13.2.2 Genetics

A genetic role in the etiology of HSCR was potentially suggested because of the increased risk in patients with Down syndrome and familial occurrence in 5–48% of patients [14–16, 20]. Kwendakwema et al. [16] reported that the occurrence rate of HAEC did not differ between children with or without Down syndrome. No genetic abnormality has been shown to cause HAEC, but a specific genotype mutation confers a higher risk for developing HAEC.

Multiple genes contributing to HSCR have been identified. Mutations of rearranged during transfection (RET), which are on the short arm of chromosome 10 and involved in the enteric nervous system [21, 22], are associated with HSCR. RET is necessary for the development of Peyer's patches, the primary inductive site for the gastrointestinal host defense, which supports this association [23].

Nucleotide oligomerization domain 2 (NOD2) is associated with Crohn disease. A study on NOD2 reported that 19.2% of patients with HAEC were carriers of NOD2 mutations compared with no patients without HAEC who had no NOD2 mutation [24].

The caudal type homeobox gene-1 and gene-2 (CDX-1 and CDX-2) encode transcription factors in endoderm-derived tissues of the intestine. Both genes and cytokines are involved in the mucosal proliferation and differentiation. These genes are expressed in the colonic mucosal epithelium in normal infants and in those with neonatal necrotizing enterocolitis and HSCR, but they are reduced in patients with HAEC [5]. The finding of reduced expression of CDX-1 and CDX-2 suggests a deficiency in mucosal healing, which may contribute to prolonged mucosal damage and subsequent development of HAEC.

The integrin beta-2 (ITGB2) immunomodulatory gene (CD18) is involved in cell-surface-mediated signaling and associated with participation of T-cell development in chronic colitis. Variations of CD18 have been found to be associated with HSCR and development of HAEC [9, 25].

Endothelin receptor B (Ednr-B) along with its ligand regulates enteric neural crest cell proliferation, migration, and differentiation. In the murine model, mutation of Ednr-B leads to aganglionosis of the distal hindgut, mimicking the most common clinical finding in patients with HSCR [26].

13.2.3 Mucosal Barrier

Mucosal barrier function is an important and fundamental component in intestinal homeostasis. Disturbed barrier dysfunction has been described in many human diseases and animal models (e.g., inflammatory bowel disease, irritable bowel syndrome, and intestinal hypersensitivity). Mucosal barrier dysfunction may result in adherence of pathological organisms to enterocytes. Goblet cells are responsible for mucus secretion in the lumen of the gastrointestinal tract, which facilitates trapping of harmful bacterial and viral pathogens [27]. The mucus layer plays a major role in maintaining the integrity of the colonic epithelium and is composed of an extracellular matrix of water and glycosylated molecules with antimicrobial properties. The outer mucus layer is the habitat of intestinal microbiota and is essential for forming the intestinal microenvironment. The inner mucus layer prevents permeation of the microbiota to deeper tissues and adherence of pathogens to enterocytes, reducing susceptibility to infection. In the steady state, bacterial invasion across the colonic epithelium prevents mucus. The colonic epithelium is composed of glycosylated proteins of the MUC family, which are secreted by goblet cells. Mucus is renewed by mucins secreted by goblet cells in the intestine, and these are mainly the secretory type MUC-2 [28–30]. Mattar et al. [31] collected stool samples from patients with HSCR and found that MUC-2 was obviously lower in the HSCR group compared with healthy controls. Interestingly, MUC-2 expression in the HAEC group could not be detected. Impaired intestinal barrier function in patients with HAEC may decrease secretion of specific mucin and increased adherence of bacteria to enterocytes.

A decreased number of goblet cells have been found in intestinal mucosa of patients with active inflammatory bowel disease. In a murine model of HAEC, Thiagarajah et al. [32] demonstrated that Ednr-B−/− mice that developed HAEC showed no change in MUC-2, but there was a reduction in membrane-bound MUC-4 in the distal colon. Moreover, Ednr-B−/− mice had a higher goblet cell number, larger size, and more proliferation in the aganglionic region compared with wild-type mice [32]. Similar results have also been

found in humans with HAEC, where overall goblet cell size was similar but intracellular acidic and neutral mucin concentrations were greatly reduced compared with control groups [27].

Recently, Tomuschat et al. [33–35] performed several studies focusing on the relationship of HAEC and an interleukin (IL)-17-mediated increased inflammatory response, interference with the intestinal epithelial barrier function by altered K (ATP) expression, and an IL-36γ-mediated increased inflammatory response in the human colon.

13.2.4 Mucosal Immunity

Innate and adaptive immunity by immune cells function together to eliminate pathogens, such as bacteria, fungi, and viruses and maintain intestinal homeostasis [18, 36–38]. Gut-associated lymphoid tissue, which consists of Peyer's patches, solitary follicles, aggregated follicles, and diffusely distributed lymphoid cells in the lamina propria of the intestine, is mainly responsible for immunity. Macrophages, dendritic cells, innate lymphoid cells, and Paneth cells are only found in the small intestine. Goblet cells and intestinal epithelial cells contribute to intestinal innate immunity and then adaptive immunity.

Immunopathological mechanisms associated with HSCR may exist. The diversity of an altered local immune response may reflect a multifactorial microbial etiology in HAEC. Imamura et al. [39] found that immunoglobulin (Ig) A- and IgM-containing plasma cells were significantly increased in the lamina propria along the entire length of resected bowel in patients with HAEC compared with patients without HAEC and controls. Luminal secretory component staining of the aganglionic segment of the colon from patients with HAEC was considerably reduced. This previous study also showed that, in the lamina propria, the numbers of CD68-positive monocyte/macrophages and CD45RO-positive leukocytes in patients with HAEC were higher compared with patients without HAEC. With regard to CD57-positive natural killer (NK) cells, there is a unique distribution pattern compared with other cell types [39]. A significantly higher amount of CD57-positive NK cells was shown only in the lamina propria of the ganglionic bowel in patients with HAEC compared with patients without HAEC. NK cell values in the ganglionic bowel of patients without HAEC and in the aganglionic bowel in all patients were similar to controls.

In the murine neural crest conditional deletion of Ednr-B (Ednr-BNCC−/−) model of HSCR, Gosain et al. [40] found impaired gastrointestinal mucosal immunity with the spleen as a potential site of the defect. The Ednr-BNCC−/− condition results in mutants with defective neural crest cell migration, distal colonic aganglionosis, and development of enterocolitis. Ednr-BNCC−/− displays lymphopenia of Peyer's patches, which are the major inductive site of gastrointestinal mucosal immunity. Peyer's patches of Ednr-BNCC−/− show decreased B-lymphocytes, specifically IgM + IgDhi (mature) B-lymphocytes, which are normally activated and produce IgA following antigen presentation. Ednr-BNCC−/− animals demonstrate decreased small intestinal secretory IgA but unchanged nasal and bronchial airway secretory IgA, indicating a gut-specific defect in IgA production or secretion. Gosain et al. [40] concluded that intestinal defects in HSCR are not restricted to the aganglionic colon, but extend proximally, even into the ganglionated small intestine and immune cells.

Moore et al. [41] assessed immunoglobulin activity in surgically resected specimens of HSCR using biochemical evaluation. Histologically, they found a significant increase in IgG and IgM in segments of the bowel that were identified as the aganglionic or transitional zone. This finding suggests an area of maximal immunological activity in the transitional zone. The lack of an increase in IgA immunoglobulin activity in the same bowel segments suggests that the IgA response may be related to an associated enterocolitis in HSCR.

Gut innervation participates in the development of the intestinal immune system. Enteric neurons innervate the intestinal mucosa, including gut-associated lymphoid tissue [42]. Evidence of inflammatory neural reflex has been found. The parasympathetic nervous system can modulate lymphoid tissues and immune cells in the intestine. Abnormality of the enteric nervous system (ENS) and parasympathetic nervous system in HSCR may play a role in the dysfunction of the intestinal immunity. Possible causes of this relationship include the effects of an antenatal infection or local microenvironmental influences on differentiation or maturation of migrating neuroblasts of the ENS.

Karlsson et al. [43] reported that Paneth cell antimicrobial peptides, including α-defensins, may play an important role in commensal microbial homeostasis. This role is in addition to their proposed role in protection against infection.

13.2.5 Microbiome

With regard to the role for the intestinal microbiome in the development of HAEC, the causative and specific pathogenic organisms of HAEC are unknown [1]. Hundreds of microbial species thrive within the gut of humans and other animals and can affect the health of their host in profound ways. Sustaining a balanced intestinal microbial community is critical for maintaining intestinal health and preventing chronic inflammation.

Recently, several studies performed 16S rRNA gene sequencing of fecal bacteria to analyze the intestinal microbiomes in patients with HAEC and HSCR. These studies

showed that the microbiota from patients with HAEC and HSCR is different in proximal and distal samples [44–46]. Li et al. [45] demonstrated that the microbiota was significantly different between patients with HSCR without HAEC (characterized by the prevalence of Bacteroidetes) and patients with HSCR and HAEC in the active phase (characterized by the prevalence of *Proteobacteria*). They also found that the microbiota of patients with HSCR and HAEC in remission was similar to that of patients with HSCR and HAEC. A dysbiosis with dominance of fungi and bacteria in the gut microbial ecosystem of patients with HSCR may develop HAEC.

Frykman et al. [46] demonstrated that bacterial composition of patients with HSCR and HAEC in the active phase showed a modest reduction in Firmicutes and Verrucomicrobia, with a higher rate of Bacteroidetes and Proteobacteria compared with that of patients with HSCR without HAEC. In contrast, the fecal fungi composition of patients with HSCR and HAEC in the active phase showed a marked reduction in diversity, with increased *Candida* sp. and reduced *Malassezia* and *Saccharomyces* sp. compared with that of patients with HSCR without HAEC. The most striking finding in patients with HSCR and HAEC in the active phase was that the *Candida* genus was segregated into "high-burden" patients (97.8%, *C. albicans*; 2.2% *C. tropicalis*) and "low-burden" patients (26.8%, *C. albicans*; 73%, *C. tropicalis*). Interestingly, even the low-burden patients with HSCR and HAEC in the active phase had an altered *Candida* community structure. In these patients, there were only two species compared with more diverse *Candida* populations in patients with HSCR without HAEC.

Pierre et al. [47] investigated whether gut microbiota and intestinal immunity changes contribute to the risk of occurrence of HAEC in an HSCR model. EdnrbNCC+/− and EdnrbNCC−/− contain similar cecal flora but then undergo reciprocal changes. EdnrbNCC−/− displays dysbiosis, impaired mucosal defense, decreased luminal secretory phospholipase A2 levels, and increased enteroinvasion of *Escherichia coli* just prior to robust colonic inflammation and death.

The gut is a highly dynamic environment, which is subject to periodic waves of peristaltic activity. Rolig et al. [48] found that zebrafish that lacked an enteric nervous system due to a mutation in the HSCR gene (SOX10) developed microbiota-dependent inflammation. This inflammation was transmissible between hosts. They showed that the enteric nervous system modulated gut microbiota community membership to maintain intestinal health.

Wiles et al. [49] demonstrated that host-mediated spatial structuring and stochastic perturbation of communities can drive bacterial population dynamics within the gut. This revealed a new facet of the intestinal host-microbe interface by demonstrating the capacity of the enteric nervous system to influence the microbiota. They hypothesized the host gut motility promotes competitive exclusion within the intestinal microbiota and tested this mechanism by measuring colonization in hosts with enteric nervous system dysfunction due to an RET mutation. In humans, this mutation is associated with the intestinal motility disorder known as HSCR.

13.2.6 Surgical Factors

Obstructive symptoms may occur after pull-through surgery. Causative factors of these symptoms include mechanical obstruction, persistent or acquired aganglionosis, hypoganglionosis, transition zone pull-through, internal sphincter achalasia, disordered motility in the proximal intestine that contains ganglion cells, or functional megacolon caused by stool-holding behavior [50].

Some children also have fever with episodes, suggesting HAEC. Postoperative intestinal obstruction may lead to stasis, bacterial overgrowth, and translocation. HAEC remains a frequent complication after surgery, such as Swenson, Duhamel, original Soave, Z-shaped anastomosis, and TAEPT procedures [1]. Minford et al. [51] reported that TAEPT and Duhamel procedures had similar medium-term functional outcomes. However, TAEPT had a high incidence of postoperative HAEC, and stricture of the pull-through segment was observed in 19% of patients.

Hackam et al. [52] reported that the incidence of postoperative HAEC was 32% in 105 consecutive patients with HSCR who were treated by the procedures of original Soave in 63, Duhamel in 17, and Swenson in 25 patients from 1991 to 1996. They concluded that the risk of postoperative HAEC was significantly increased by mechanical factors related to anastomotic complications, such as stricture or leakage, and postoperative intestinal obstruction. Thakkar et al. [15] reviewed postoperative functional outcomes of surgical cases between 2002 and 2014. All of their patients, except for two (original Soave procedure), underwent the Duhamel pull-through procedure, and HAEC occurred in 15% patients in whom approximately 50% had multistage surgery. Postoperative obstructive defecation after surgery from constipation to HAEC occurs in up to 30% of children with HSCR [20, 53, 54].

Recently, Langer et al. [50] proposed guidelines with an algorithm for investigation and management of postoperative obstructive symptoms in children with HSCR after pull-through. They showed that this stepwise, logical approach to diagnosis and management of postoperative obstructive symptoms following pull-through for HSCR could facilitate treatment. They emphasized that important examinations for decision-making are rectal examination and contrast enema, rectal biopsy, and motility workup. They then recommended selecting therapeutic options, such as dilatation or revisional

surgery, redo pull-through surgery, botulinum toxin injection, bowel management, stoma creation, antegrade colonic enema, and colonic resection.

13.2.7 Other Factors

The colonic microbiota is necessary for short-chain fatty acid (SCFA) production. Demehri et al. [55] showed that a complex interplay between the colonic metabolome and changes in the microbiota may affect the pathogenesis of HAEC. This is because children with a history of HAEC have reduced fecal SCFA levels and the SCFA profile is altered, with reduced acetate and increased butyrate levels.

13.3 Diagnosis

Clear definitions of HAEC are lacking in the literature. In the clinical history and physical manifestation of patients, the classic manifestations of HAEC include diarrhea, abdominal distension, vomiting, explosive expulsion of flatus, and liquid feces on a rectal examination, abdominal pain, pyrexia, lethargy, rectal bleeding, bowel perforation, and shock [6]. Abdominal radiographs may show a distended loop of the colon often associated with small bowel dilation and/or multiple air fluid levels. There may be thickening of the bowel wall and mucosal irregularity, and if perforation occurs, pneumoperitoneum is observed. These symptoms are nonspecific and may lead to delays in accurate diagnosis and treatment. This reflects the wide range in incidence of HAEC reported among different surgical groups in the literature [1, 4, 6–13].

Pastor et al. [56] developed an HAEC score for diagnosing HAEC through a consensus approach using the Delphi method. This was achieved by identifying clinical diagnostic criteria for HAEC from a larger pool of potential items. HAEC scores consist of four large categories, including the clinical history, physical examination, radiological examination, and laboratory data. Each category consists of 2–5 items, with a total of 16 items. The items of diarrhea with explosive stool, diarrhea with foul-smelling stool, explosive discharge of gas and stool in a rectal examination, and a distended abdomen received two points each. The other 12 items received 1 point each. The highest score is 20 and a score $\geq$10 points was diagnosed as HAEC.

In 2017, Gosain et al. [8] proposed guidelines for the diagnosis and management of HAEC. They categorized clinical suspicion and severity of HAEC into three grades. These grades included grade I (possible HAEC), grade II (definite HAEC), and grade III (severe HAEC) based on the clinical history, physical examination, and radiographic findings. This guideline is not intended as a scoring system but rather a decision-support tool, which is a staging system similar to that described by Bell for necrotizing enterocolitis [57]. The best practice for improved outcomes is suspicion and early recognition of HAEC in a possible or mild stage and preventative practices.

13.4 Management

Management for HAEC is relatively non-specific and consists of bowel rest, rectal irrigation, and antibiotic administration. Bowel rest and dietary therapy, such as oral hydration, nothing per os, and intravenous fluid applied to patients, are selected depending on symptoms from mild to severe. Antibiotics that are administered are selected empirically in HAEC, such as metronidazole or a broad-spectrum coverage regimen. Rectal irrigation is performed against fecal stasis and bacterial overgrowth. Decompression of the colon is essential and can generally be performed with rectal washouts. However, in the case of fulminant disease, washouts should be avoided because of the risk of perforation [4]. Inability to adequately decompress the bowel or cases of sepsis or perforation may be an indication for proximal enteric diversion. If possible, intraoperative frozen section histology should be performed to determine the level at a site with normal ganglion cells in the small intestine and colon.

Gosain et al. [8] also proposed guidelines for managing HAEC based on grading of HAEC. By grading from grade I (possible HAEC) to grade III (severe HAEC), considerations for disposition for outpatient or inpatient care or intensive care unit, diet, antibiotics, nasogastric decompression if there is considerable abdominal distension, rectal irrigation, and the need for surgery are listed. In cases classified as grade I, close monitoring is necessary if symptoms progress to a higher grade of disease. In children with findings consistent with grade III (severe) HAEC, they suggest that pneumoperitoneum rarely occurs, which would require immediate surgical intervention.

Risk factors for HAEC after pull-through surgery include anastomotic leak or stricture and postoperative intestinal obstruction due to adhesions. Such factors increase the relative risk of subsequent enterocolitis by approximately threefold [4, 52, 58]. Ruling out a mechanical cause of partial bowel obstruction should be undertaken in infants who present with repeated episodes of enterocolitis following a pull-through procedure. If a contrast enema is normal, full-thickness rectal biopsy is warranted to rule out aganglionosis in the pull-through segment [59, 60]. In cases of retained or secondary aganglionosis, which is a rare cause of HAEC, patients will require a redo pull-through [61]. In cases of anastomotic stricture, a trial of dilation is recommended with the possibility of a redo pull-through being reserved if dilations are unsuccessful. If there is no

anatomical or pathological cause identified, non-relaxation of the internal anal sphincter may be the cause of stasis with obstructive symptoms and recurrent HAEC in some patients. This situation can be confirmed by anorectal manometry. Injection of *Clostridium botulinum* toxin (Botox; Allergan plc, Dublin, Ireland) into the intersphincteric groove decreases the rate of hospitalization for postoperative obstructive symptoms in children with HSCR [62]. Internal anal sphincter (IAS) achalasia is a clinical condition with presentation similar to HSCR but with the presence of ganglion cells on rectal suction biopsy. Friedmacher et al. [63] performed a meta-analysis to compare the efficacy of posterior IAS myectomy and intrasphincteric botulinum toxin (Botox) injection for treating IAS achalasia. IAS achalasia was diagnosed based on the results of anorectal manometry and rectal suction biopsy. They concluded that in patients with IAS achalasia, posterior IAS myectomy appears to be a more effective treatment option compared with intrasphincteric Botox injection. A recent study reported that Botox injection procedures that were performed with ultrasound guidance resulted in greater short-term improvement than without ultrasound (76% versus 65%) and there was less requirement of a definitive surgical therapy for obstructive defecation ($p < 0.05$) [53]. In children with recurrent HAEC, more than 1–2 years following their pull-through, the use of posterior IAS myectomy should be considered [64].

13.5 Prevention

Prevention for HAEC is the best solution. Some authors have advocated the use of preventive measures in selected patient populations [65]. However, unfortunately, there is no definitive evidence to support the routine use of several preventive measures [4].

Rectal washouts limit colonic distention and fecal stasis and should be performed when surgical management is delayed [6]. Postoperatively, scheduled rectal washouts reduce the incidence of postoperative HAEC. A review of the literature showed that 36% of patients in the nonirrigation cohort developed postoperative enterocolitis compared with 8% of patients in the rectal irrigation cohort [66]. Traditionally, routine anal dilations were thought to prevent stricture formation, with most pediatric surgeons recommending daily dilations by parents. However, recent data have challenged this assertion. A retrospective review by Temple et al. [67] showed that children undergoing repair of HSCR or anorectal malformation had either routine dilatation by parents or weekly calibration of an anastomosis by the surgeon. Daily dilation was reserved for children with the concern of anastomotic narrowing. There was no significant difference in the development of enterocolitis in children with HSCR with or without anastomotic narrowing.

Probiotics potentially play a protective role in maintaining intestinal mucosal integrity by the interaction between the microbiome and epithelial cells. Two prospective, multicenter, randomized, placebo-controlled trials on whether oral probiotics could decrease the incidence and severity of HAEC were performed. Wang et al. [17] used oral *Bifidobacterium*, *Lactobacillus acidophilus*, and *Enterococcus* triple viable capsules. They found that probiotics not only significantly diminished the incidence but also decreased the severity of HAEC. Moreover, they also showed that probiotics decreased pro-inflammatory cytokine levels and increased anti-inflammatory cytokine levels, as well as balanced T lymphocytes. El-Sawaf [10] performed a study that used oral VSL#3 (VSL Pharmaceuticals, Inc., Ft. Lauderdale, FL). VSL#3 is a probiotic preparation containing 90 billion viable lyophilized bacteria (per packet) composed of four strains of *Lactobacillus*, three strains of *Bifidobacterium*, and one strain of *Streptococcus salivarius* subsp. *thermophilus*. They found that the incidence of HAEC was not reduced with prophylactic probiotics. Therefore, effectiveness of probiotics for preventing the occurrence of HAEC is controversial, and more studies are required.

Prato et al. [7] suggested prevention strategies for the occurrence of HAEC. Preoperatively, they recommended intensive bowel management and frequent reassessment for neonates with HSCR and awareness of guardians about the occurrence of HAEC. In particular, patients with associated congenital heart malformations are fragile and should be considered for creation of prophylactic enterostomy by considering their fetal risk of HAEC. Radical surgery (pull-through) should be performed as soon as possible after diagnosis.

Postoperatively, patients with severe comorbidities should undergo strict clinical follow-up. These patients should also receive daily rectal irrigations with 10 ml/kg of normal saline for 6 months postoperatively to prevent HAEC [68]. Prato et al. [7] strongly suggested that the most important factor in prompt and effective treatment of complications of HAEC is education of guardians for adequate bowel management during the hospital stay. Additionally, there should be instruction on how to deal with acute onset of diarrhea, fever, abdominal distension, and vomiting, before hospital referral [7].

13.6 Summary

HAEC is the most common complication of HSCR. HAEC manifests clinical symptoms that range from mild to severe. HAEC sometimes becomes serious and life-threatening. Historically, surgical procedures for HSCR have greatly progressed, but HAEC remains a frequent complication

before and after surgery. The pathogenesis of HAEC is complex, and diagnostic strategies have not been established. Further studies are required to prevent this condition.

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Differential Diagnosis

14

Aya Tanaka and Ryuichi Shimono

14.1 Introduction

Hirschsprung's disease (HD) in neonates causes symptoms such as abdominal distention, bilious vomiting, or impaired meconium excretion, and the differential diagnosis includes various diseases with similar symptoms. Anamnesis, physical findings, and complementary evaluations such as abdominal plain X-rays and contrast enema imaging, anorectal manometry and suction, or surgical biopsy are generally needed for a definitive diagnosis. It should be noted that findings of complementary evaluations (e.g., barium enemas, recto-anal reflex, and biopsy) occasionally lead to misdiagnosis in early neonates, particularly in those with a low birth weight. Also, some conditions such as hypothyroidism, myopathy, or neuropathy cause motility disorders of the gastrointestinal tract that need to be included in the differential diagnosis.

14.2 Congenital Intestinal Obstruction

Neonates with complete atresia or stenosis of the colon or distal small intestine will also present with small intestinal or colonic obstruction, the symptoms of which may initially mimic HD. Radiological imaging such as abdominal plain X-rays, contrast enema, or upper gastrointestinal series are used for differential diagnosis as necessary. The number of dilated loops filled with intestinal gas or intestinal contents observed in abdominal plain X-ray films differs with the location of the obstruction, similar to the location of the aganglionic area. Barium contrast enemas frequently show microcolon without caliber change at the transitional zone in patients with congenital intestinal obstruction. The first stool following birth (meconium) is often pale in color, but that is not always the finding in patients with intestinal obstruction.

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Intestinal obstruction is sometimes observed in neonates or infants as a midgut volvulus related to malrotation. Generally, the onset of midgut volvulus is more acute than that of HD, and it tends to result in short gut syndrome. It is thus important to determine whether patients with bilious vomiting have a midgut volvulus or not. The finding of Treitz' ligament dysplasia and malpositioning of the vermiform appendix in a gastrointestinal series or contrast enema are helpful in the diagnosis of malrotation. HD may be associated with either colonic or intestinal obstruction [1, 2], and HD-like findings may be observed in the small intestine during surgery regardless of the preoperative diagnosis of HD. In those patients, rapid intraoperative pathological confirmation and switch to an alternative surgical procedure are required.

14.3 Anorectal Malformations

In neonates, anorectal malformations frequently exhibit HD-like symptoms. Most cases can be differentiated from HD by visual inspection and digital examination of the anal perineal area. Rectal atresia or stenosis is a rare condition in the series of anorectal anomalies, although barium enema is useful for the diagnosis. Most patients need prompt anorectal drainage, anal plasty, or colostomy before accurate diagnosis of the subtype to avoid clinical complications caused by intestinal obstruction. Infants with chronic constipation sometimes present as outpatients. The perineal anal area must be carefully examined because lower anal anomalies such as covered anal stenosis or ano-cutaneous fistulae may cause constipation. Anorectal anomalies are occasionally accompanied by an imperforated anus [3, 4].

14.4 Meconium-Related Ileus

Bowel obstruction caused by meconium retention in neonate is generally classified into meconium ileus, meconium plug syndrome, and meconium disease. Meconium ileus is caused

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by abnormal external secretion accompanied with cystic fibrosis [5]. All three diseases can be in the same category at the point of presenting functional bowel obstruction. Conditions with this etiology include meconium plug syndrome, meconium disease, and meconium ileus, but the defining criteria are varied, and the three conditions may be confused with HD. In the literatures, meconium disease is a more severe condition than meconium plug syndrome. Meconium plug syndrome tends to exhibit milder symptoms with well response to conservative therapy. Therefore, the condition is not usually recurrent. Small left colon syndrome is historically reported as a type of meconium plug syndrome and is associated with a finding of a caliber change at the splenic flexure of the colon [6]. In meconium plug syndrome, the meconium is reported to have an elevated protein level and altered enzyme activity, suggesting that the obstruction is caused by an immobile luminal obstruction rather than mural constriction and diminished peristalsis [6]. On the other hand, meconium disease exhibits more severe symptoms followed by longer clinical course. Patients with meconium disease may require surgery because of lack of resolution following conservative therapy. There is considerable clinical and radiological overlap among the three types of meconium-related diseases, although meconium ileus is more clearly defined. Thus, Kubota propounds that we should call these functional bowel obstruction "medonium-related ileus" [7]. The cause of meconium-related ileus is believed to be immaturity of the myenteric plexus and inadequate peristalsis [7, 8].

Symptoms of meconium-related ileus, a blockage caused by meconium, such as abdominal distention, bilious vomiting, or delayed meconium passing, are similar to those of HD.

Clinically, there is abdominal distension without peritonitis in patients with the condition. Radiological evaluation shows distended intestinal loops without air-fluid boundaries and with little or almost no rectal gas. Contrast enema findings include microcolon or thick meconium, most often in the distal ileum. As it can also be the first sign of HD, radiological studies, anorectal manometry, and rectal biopsy by suction should be considered to rule out this pathology.

Recent increases of very low birth weight and extremely low birth weight neonates have made it more likely to encounter meconium-related ileus. A water-soluble contrast enema is usually used for both diagnostic and therapeutic [9]. Anorectal manometry and biopsy are generally reserved for patients who remain constipated.

Meconium ileus accounts for approximately 30% of the cases of intestinal obstruction in neonates [10]. It is often the first manifestation of cystic fibrosis and occurs in approximately 20% of patients diagnosed with cystic fibrosis [11]. Cystic fibrosis results from mutations in the *CFTR* gene, which codes for a cell membrane protein termed the cystic fibrosis transmembrane (conductance) regulator (CFTR). An abnormal CFTR protein results in altered electrolyte content in the extracellular environment of the apical surface of epithelial cell membranes. This leads to desiccation and reduced clearance of secretions from tubular structures lined by affected epithelia. In sweat glands, CFTR dysfunction leads to inadequate resorption of sodium, chloride, and potassium [12].

There are two types of meconium ileus—simple and complex. In simple meconium ileus, viscid meconium physically obstructs the terminal ileum and the small intestine proximal to the obstruction, which then becomes dilated with additional meconium, gas, and fluid. In complex meconium ileus, the meconium-distended segments of the ileum can give way to complications such as prenatal volvulus, ischemic necrosis, intestinal atresia, or perforation with extrusion of the meconium into the peritoneum [11].

In meconium ileus, abdominal distention is usually present at birth. Within hours, as air is swallowed, the distention increases, and the infant vomits bile-stained material. Thickened intestinal loops are often palpable and visible through the abdominal wall. Massive distention and abdominal tenderness or erythema indicates the presence of complications [10]. A plain radiograph demonstrates dilated small intestinal loops with inspissated meconium in the distal ileum and large intestine. The classic "soap-bubble" sign seen when meconium mixes with swallowed air may be apparent in the distal small intestine. Plain radiography is also indicated to assess for perforation, calcifications (evidence of prenatal perforation and meconium peritonitis), or other abnormalities. Evidence of perforation indicates complex meconium ileus and precludes an attempt at nonoperative decompression. Infants with evidence of perforation should proceed directly to surgery [11, 13]. Contrast enema typically reveals an unused, small caliber microcolon, and contrast refluxed into the terminal ileum outlines multiple filling defects consistent with meconium pellets. Gastrografin is a frequently used water-soluble hyperosmolar contrast agent with a reported 40% rate of successful acceleration of meconium evacuation [13, 14].

14.5 Chronic Constipation

Functional constipation is a common problem in childhood and has an estimated worldwide prevalence of 3% [15]. When evaluating constipation, it is important to determine the age at symptom onset. Onset in infants of <1 month of age should increase the suspicion of an organic condition such as HD [16]. The timing of passage of the first meconium is especially relevant to the possibility of HD; a delay of 48 h in a full-term neonate suggests the need for definitive testing to rule out a diagnosis of HD [17].

A careful medical history should be obtained to identify possible organic causes of constipation. Functional constipation is almost always the diagnosis in children >1 year of

age. The passage of infrequent, large-caliber stools is highly suggestive of functional constipation. Fecal soiling, especially sometime after a child has been toilet trained, suggests rectal impaction from functional constipation. One study found that 78% of children with encopresis had fecal impaction, and approximately three of every four children with constipation have pain on defecation. When evaluating children with constipation, family physicians should ask about toileting behavior, such as the timing of intestinal movements, postures suggestive of stool retention (e.g., standing with legs crossed, rocking, or squeezing the gluteal muscles), possible restricted access to toilets, and toilet avoidance or refusal [18].

A digital rectal examination should be performed to determine rectal tone. The finding of rectal impaction may confirm the diagnosis of functional constipation. The presence of anal fissures or papillae indicative of chronic anal fissures also suggests functional constipation. Further evaluation is indicated in children with poor response to conventional treatment, delayed meconium passage, abdominal distention, colitis, or intractable constipation despite strict adherence to therapy. Laboratory studies can be performed to evaluate the patient for systemic diseases, such as thyroid or other metabolic diseases, celiac disease, or lead toxicity. Motility studies, such as anorectal manometry, can be used to detect sphincter abnormalities, such as HD or a nonrelaxing internal anal sphincter. Magnetic resonance imaging of the spine can reveal a tethered cord, spinal cord tumor, or sacral agenesis. A trial of a cow's milk-free diet may also be considered because constipation can be caused by intolerance to cow's milk, especially in young children with anal fissures [19].

14.6 Food Allergy

Neonatal and infantile gastrointestinal (GI) allergy causes digestive symptoms such as emesis, hematochezia, and diarrhea in neonates and infants. This type of allergy is a cell-mediated reaction that occurs independent of IgE. The most common causative food is cow's milk. Children who are exclusively breast-fed may develop this disease. The number of reported cases has increased rapidly in the last 10 years [20]. Cow's milk allergy (CMA) is not rare in infancy; the prevalence has been estimated as 2.0%–7.5%. GI symptoms caused by CMA are often overlooked because of their diversity and insidious nature [21]. In addition to the symptoms noted above, GI allergy may also present with HD-like symptoms such as severe abdominal distention and/or constipation. Allergic colitis can affect any part of the colon, but the rectosigmoid is often the primary segment involved. The radiologic findings in some cases show irregular narrowing of the rectum and a transitional zone on barium enema similar to those of HD [14, 21–23]. The mucosa is friable, with foci of erythema separated by regions of normal-appearing colon. Erosions and ulcerations can simulate an infectious etiology. A rectal suction biopsy may be the most accurate confirmatory test [23].

Allergen-specific lymphocyte stimulation tests are positive in most patients with suspected GI allergy. This test indicates that the allergy is cell-mediated. The diagnosis is based on development of digestive symptoms by after causative food ingestion, disappearance of symptoms by eliminating causative foods, and a positive food-challenge test. The prognosis is favorable, with approximately 70% of patients acquiring food tolerance by 1 year of age. Approximately 90% acquire tolerance by their second birthday.

Compared to patients with HD, those with allergic colitis tend not to experience vomiting. Presentation of symptoms occurs later in GI allergy patient than in those with HD and reflects the timing of transition to cow milk feeding [14]. Because the incidence of cow's milk allergy mimicking HD is relatively high, it should be considered even in breast-fed babies.

14.7 Allied Disorders Including Pseudo-Hirschsprung's Disease

The details of allied disorders are discussed in other chapters in Part II and are not described here. Allied disorders should be differentiated from HD and are usually divided into conditions with normal or abnormal ganglion cells. In nearly all allied disorders, HD-like symptoms start when the patients are neonates, and most require full-thickness biopsy during patient evaluation.

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Nationwide Survey of Japan in Hirschsprung's Disease

15

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15.1 Background

We previously performed three nationwide surveys of the cases treated between 1978 and 1982 (Group 1) [1], between 1988 and 1992 (Group 2), and between 1998 and 2002 (Group 3) [2]. To clarify the changing profile of Hirschsprung's disease (HD) in Japan, we carried out a fourth nationwide survey for the cases between 2008 and 2012 (Group 4) [3] and compared these findings with those of the previously performed studies (Groups 1, 2, and 3).

In the last few decades, the early diagnosis and appropriate pre- and postoperative management of HD, including medical and surgical treatments, have undergone various changes. In particular, the introduction of transanal endorectal pull-through (TAEPT) [4] and laparoscopy-assisted operations [5, 6] has enabled HD operations to be performed without utilizing a large-sized laparotomy, which has led to not only safe and reliable perioperative outcomes but also cosmetic improvements and expectations of a good quality of life.

15.2 Nationwide Survey Across Four Decades

In the current nationwide retrospective cohort study (Group 4), which was supported by the Ministry of Health and Welfare, Japan, questionnaires consisting of an individual patient form with questions on the general incidence, diagnosis, and treatments of HD were sent to 156 departments of pediatric surgery at major universities and hospitals throughout Japan [3]. The study population was limited to the cases treated during the 5-year period from 2008 to 2012, and that were ultimately diagnosed as HD definitively with a histopathological examination of resected specimens. The completed forms of 1087 patients were sent back from 147 universities and hospitals (94.2%), including almost all of the major pediatric surgery departments in Japan. Each case was registered on the web. These data (Group 4) were compared with the previous collected data of 1628 patients between 1978 and 1982 (Group 1), 1121 patients between 1988 and 1992 (Group 2), and 1103 patients between 1998 and 2002 (Group 3). Ultimately, a total of 4939 cases were evaluated (Table 15.1).

This retrospective study was performed according to the Ethical Guideline for Clinical Research published by the Ministry of Health, Labour and Welfare of Japan on July 30, 2003 (revised 2008), and complied with the 1964 Declaration of Helsinki (revised in 2008). The study was approved by the Ethics Committee for Clinical Research of Faculty of Medical Sciences, Kyushu University (approval number: 27-273).

15.3 Epidemiology and Genetics

The estimated incidence rates of HD based on the annual number of cases divided by the annual number of newborns from annual report provided by the Ministry of Health and Welfare, Japan (www.mhlw.go.jp/toukei/saikin/hw/jinkou/kakutei12/dl/04_h2-1.pdf), were 1/4697, 1/5544, 1/5343, and 1/4895 (Table 15.1). In 2008, Haricharan et al. reported that the California Birth Defect Monitoring Program survey from 1983 to 1997 identified HD in 2.8 children per 10,000 live births in Asians, 2.1 per 10,000 live births in African-Americans, 1.5 per 10,000 live births in Whites, and 1 per 10,000 live births in Hispanics [7]. The incidence of HD in Japan has been estimated to be approximately 1 in 5000 live

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Table 15.1 Summary of cases

	Group 1	Group 2	Group 3	Group 4	Total
Study period	1978–1982	1988–1992	1998–2002	2008–2012	–
Number of patients	1628	1121	1103	1087	4939
Estimated incidence	1/4697	1/5544	1/5343	1/4895	1/5077
Low birth weight (<2500 g)	5.5%	6.5%	10.4%	13.7%	8.6%
Male/female	3.0:1	3.4:1	3.0:1	2.9:1	3.4:1
Familial history	3.0%	2.8%	6.0%	7.1%	4.5%
Associated anomalies	11.1%	16.3%	21.2%	18.9%	16.3%

births over the past four decades, which is similar to the generally accepted incidence. The male-to-female ratio in Japan has remained unchanged over the last four decades.

The male/female ratios were 3.0:1, 3.4:1, 3.0:1, and 2.9:1 in Groups 1, 2, 3, and 4, respectively (Table 15.1). The percentage of patients with a birth weight <2500 g gradually increased to 13.7% compared with 5.5% in Group 1, 6.5% in Group 2, and 10.4% in Group 3. The patients with a family history of HD also increased to 7.1% in Group 4 versus 3.0% in Group 1, 2.8% in Group 2, and 6.0% in Group 3 (Table 15.1). The percentage of Japanese patients with a family history of HD has increased over the past two decades, in comparison to the two previous decades, suggesting that the HD patients reached adulthood, married, and birthed infants with HD.

The incidence of associated anomalies in Group 4 was estimated to be 18.9%, which was higher than in Groups 1 (11.1%) and 2 (16.3%) but almost equal to Group 3 (21.2%) (Table 15.1). Down syndrome (12.1%) and cardiac anomalies (11.6%) were the most commonly associated abnormalities. Genetic mutations were found in 6 of 20 patients who underwent genetic analyses; the results were as follows: *PHOX2B* (n = 3), *SOX10* (n = 1), *ZFHX1B* (n = 1), and *GATA1* (n = 1). No *RET*, *EDNRB*, or *END3* gene mutations were detected. Although this study included a genetic examination, only a small number of patients underwent a genetic analysis. No mutations of the *RET*, *EDNRB*, or *END3* genes were found in this study. However, a *PHOX2B* gene mutation was detected in three patients. In the near future, genomic analyses, including whole-gene sequestration, should be performed in order to identify mutations of the genes associated with HD and develop new therapeutic approaches for HD.

15.4 The Extent of Aganglionosis

Aganglionosis was classified into the following five categories based on the extent of the aganglionic segment:

1. Lower rectum: aganglionosis restricted to the lower rectum (under peritoneal reflection).
2. Sigmoid colon: aganglionosis extending to the sigmoid colon.
3. Left-right colon: aganglionosis extending beyond the sigmoid colon but not reaching the cecum.
4. Total colon: aganglionosis limited to the total colon and 30 cm of the terminal ileum.
5. Small intestine: aganglionosis extending orally to more than 30 cm of the terminal ileum.

The ratio of the sigmoid colon, left-right colon, and total colon increased to 63.1%, 14.9%, and 7.9% in Group 4, respectively, versus 51.9%, 13.0%, and 7.9% in Group 3 (Fig. 15.1).

15.5 Diagnostic Tools and Preoperative Management

A contrast enema was used in the diagnosis of almost all of the patients in Group 4 (99.2%); the percentage in the other groups was almost the same (95.8% in Group 1, 93.9% in Group 2, and 98.5% in Group 3). Manometry was performed less frequently in Group 4 (45.8%) than in the other three groups (64.7% in Group 1, 68.7% in Group 2, and 66.1% in Group 3). A rectal mucosal biopsy with acetylcholinesterase (AChE) staining obviously increased over time; the rates were 28.7%, 62.1%, 74.8%, and 81.8% in Groups 1, 2, 3, and 4, respectively (Table 15.2). Regarding the methods of the definitive diagnosis, a rectal mucosal biopsy with AChE staining has become popular and was used in 81.8% of the cases in Group 4, trailing just behind a contrast enema, which was used in 99.2% of the cases in Group 4. This relatively high frequency of use is because a rectal mucosal biopsy (with suction or punch) is considered to be accurate and safe [8, 9] and because AChE staining has shown high sensitivity and high specificity in the diagnosis of HD [10, 11]. Thus, the combination of a contrast enema and rectal mucosal biopsy with AChE staining is likely to become the standard method of diagnosing HD.

The percentage of patients who were definitively diagnosed at less than 12 months of age in Group 4 was 88.4%. This was almost equal to the proportions in the other groups (83.4% in Group 1, 87.3% in Group 2, and 95.3% in Group 3) (Table 15.3).

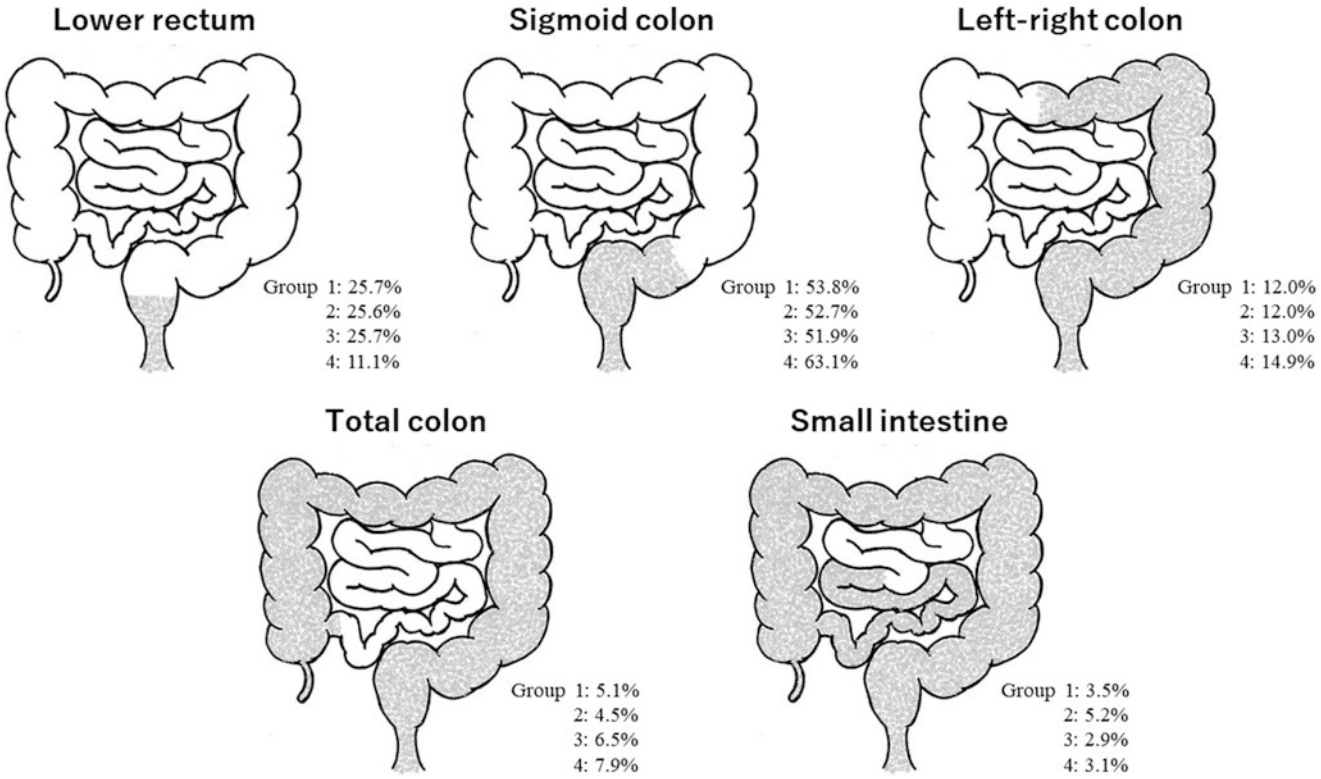

Fig. 15.1 The extent of aganglionosis

Table 15.2 The diagnostic tools

	Group 1, %	Group 2, %	Group 3, %	Group 4, %
1. Contrast enema	95.8	93.9	98.5	99.2
2. Manometry	64.7	68.7	66.1	45.8
3. Rectal mucosal biopsy (acetylcholinesterase)	28.7	62.1	74.8	81.8
4. Rectal full-thickness biopsy	23.5	12.9	13.2	20.0

The incidence of preoperative enterocolitis markedly decreased to 17.2% in Group 4, in comparison to 29.2% in Group 1 and 29.1% in Group 2, with no remarkable difference in Group 3 (17.3%). The rate of mortality caused by preoperative enterocolitis was obviously decreased to 0.3% in Group 4 versus 6.5% in Group 1, 4.9% in Group 2, and 0.7% in Group 3 (Table 15.3). The average age at the definitive operation (excluding patients older than 15 years of age) was 324.3 days in Group 4, which was younger than the average age of the patients in Groups 1 (564.8 days), 2 (464.7 days), and 3 (368.1 days). Almost 80% of the patients received definitive surgery at less than 1 year of age (Table 15.3).

Table 15.3 The preoperative status

	Group 1	Group 2	Group 3	Group 4
Timing of definitive diagnosis				
<1 month	48.7%	53.4%	40.1%	38.8%
<4 months	72.1%	76.0%	70.2%	72.5%
<12 months	83.4%	87.3%	95.3%	88.4%
Incidence of preoperative enterocolitis	29.2%	29.1%	17.3%	17.6%
Mortality in preoperative enterocolitis	6.5%	4.9%	0.7%	0.3%
Creation of enterostomy	68.7%	59.3%	35.2%	24.4%
Average age at a definitive operation (days)[a]	564.8	464.7	368.1	324.3

[a]Patients older than 15 years of age were excluded

15.6 Definitive Surgical Procedures

Regarding the optimal operative procedures, TAEPT was the most common procedure. It was performed in 49.6% of the cases of Group 4 (Fig. 15.2a). The rate of laparoscopy-assisted procedures increased remarkably to 46.9% in Group 4, versus 29.7% in Group 3, and 0% in Groups 1 and 2. Regarding the increase in the rate of TAEPT, Fig. 15.2b

shows that the "Soave" (original and modifications) increased to 73.1% in Group 4, versus 26.3% in Group 1, 20.7% in Group 2, and 47.4% in Group 3. The rate of primary operations without enterostomy increased to 75.6% in Group 4, versus 31.3% in Group 1, 40.7% in Group 2, and 64.8% in Group 3. Over the past two decades, the TAEPT procedure has become the most common definitive surgical treatment for HD in Japan. In addition, laparoscopy-assisted operations, including laparoscopy-assisted Duhamel's operation, laparoscopy-assisted Soave's operation, and laparoscopy-assisted TAEPT, were performed in approximately half of the patients in Group 4. In their meta-analysis, Zhang et al. reported that laparoscopy-assisted operations are generally safer and more reliable than laparotomy operations for HD [12]. In the present study, the rate of minimally invasive surgeries, including laparoscopy-assisted operations and TAEPT, increased from 29.7% and 28.6% in Group 3 to 46.9% and 49.6% in Group 4, respectively. For this reason, the average age at which patients received a definitive operation (excluding patients older than 15 years of age) has become younger over time as the perioperative safety and reliability has increased.

TAEPT was first reported by De la Torre et al. in 1998 [4], who described making a circumferential incision 1 cm above the dentate line in the rectal mucosa as a first step in transanal mucosectomy. Miyano et al. compared the medium-term postoperative outcomes in patients who received rectal mucosal dissection starting directly on the

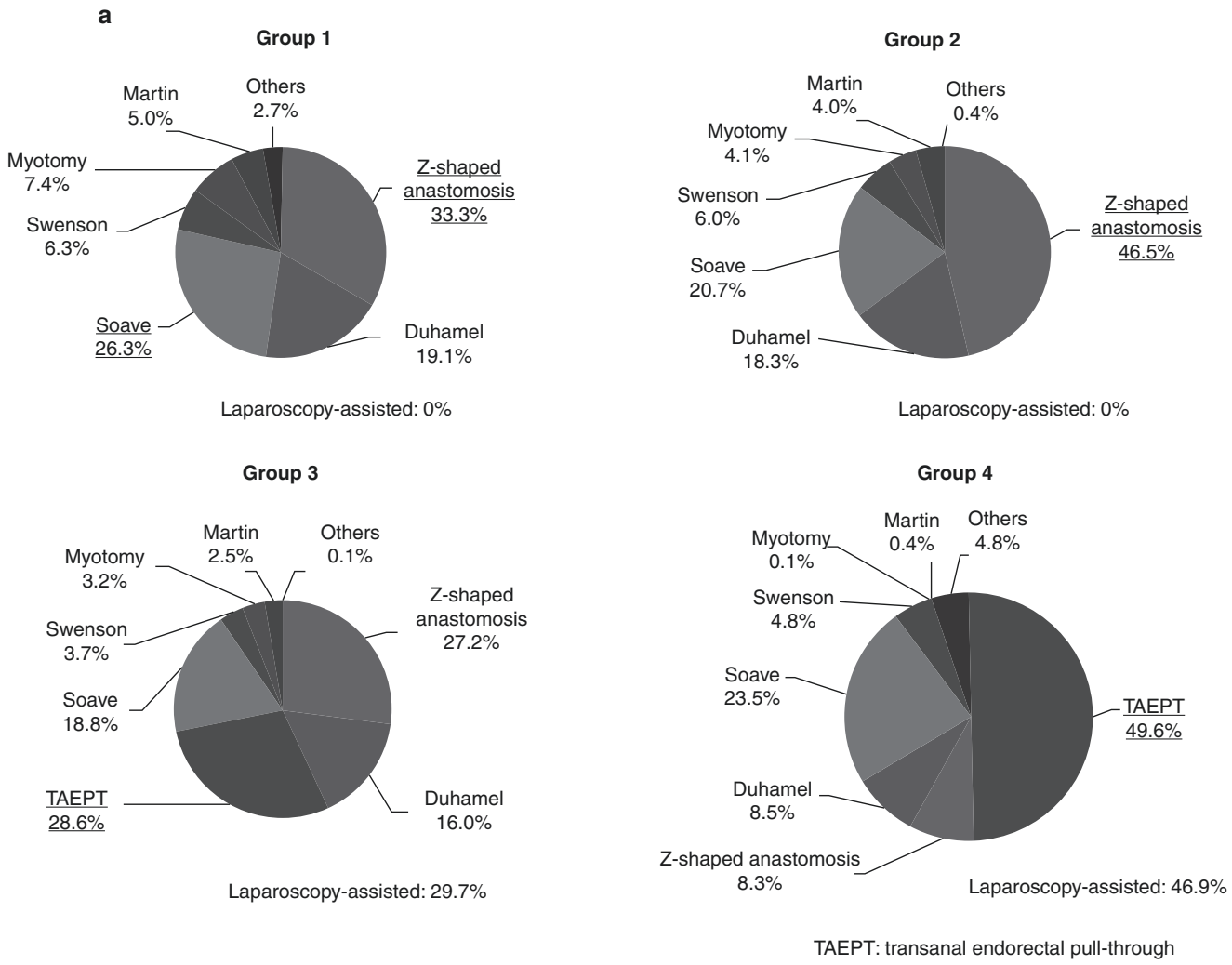

Fig. 15.2 (**a**) The definitive surgical treatments. *Duhamel* includes the original and modified procedures, except for Z-shaped anastomosis. *Soave* includes the original and modified procedures, except for TAEPT. *Swenson* includes the original and modified procedures. *Myotomy* includes myotomy and myectomy. (**b**) Classified into three basic procedures (Soave, Duhamel, Swenson). "Soave" includes the original and modified procedures and TAEPT. "Duhamel and modifications" include the original and modified procedures, Z-shaped anastomosis, and the Martin procedure

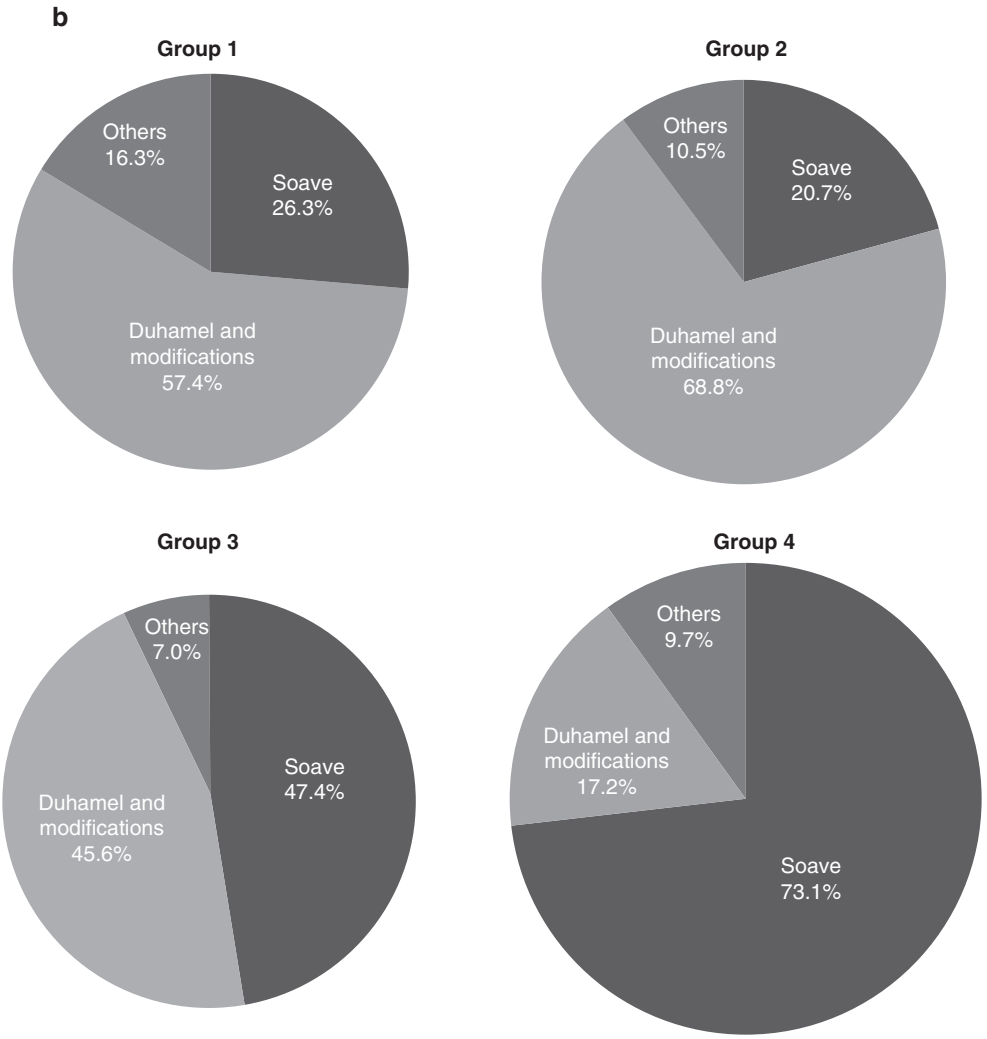

Fig. 15.2 (continued)

dentate line with those inpatients for whom rectal mucosal dissection was performed above the dentate line in laparoscopy-assisted TAEPT [13]. They found that the medium-term postoperative fecal continence was better when the anorectal line was used as the landmark for rectal mucosal dissection. In the present study, we surveyed the location from which mucosal dissection was started in TAEPT in Japanese patients. We found that the locations of the starting line varied. The proportion of surgeries performed between 0 and 4 mm was 52.1% and between 5 and 10 mm was 46.7%. In this study, the impact of the site from which rectal mucosal dissection commenced on the postoperative fecal function after TAEPT was unclear. We may examine the postoperative long-term bowel function from the standpoint of the starting line of mucosal dissection in the future. Recently, the long-term outcomes and quality of life after definitive operations for HD have been the focus of discussion [14–20]; however, no studies have compared cases in which rectal mucosal dissection started above the dentate line according to the postoperative functional outcomes after TAEPT with or without laparoscopy. Further long-term comparative studies or prospective randomized controlled studies are needed to clarify the best point from which to commence rectal mucosal dissection, with regard to the postoperative bowel function, including fecal continence and constipation, and quality of life.

15.7 Mortality

The mortality rate decreased over time to 2.4% in Group 4. Over the last decade, there has been a remarkable improvement in the mortality rate associated with the small intestine (aganglionosis extending orally to more than 30 cm of the terminal ileum). The rates were 25.5% in Group 4, 53.6% in Group 1, 33.3% in Group 2, and 35.5% in Group 3. In addition, the mortality rates of the remaining aganglionosis subgroups also improved (Table 15.4).

Table 15.4 The mortality

	Group 1, %	Group 2, %	Group 3, %	Group 4, %
Overall mortality	7.1	4.9	3.0	2.4
Mortality and the extent of aganglionosis				
Rectum-right colon	4.1	3.2	1.4	0.9
Total colon	30.4	8.0	7.1	4.2
Small intestine	53.6	33.3	35.5	25.0

The overall mortality rate and the mortality rates of each subgroup (rectum-right colon, and total colon) decreased to a satisfactory extent over time. In contrast, although the mortality rate of the small intestine aganglionosis subgroup showed a gradual decrease over time, it remained at a relatively high 25% in Group 4. The development of management strategies that can be applied before and after definitive operations, including parenteral and enteral nutrition, and probiotics [21] might have contributed to the decreased mortality rate in this subgroup compared with Group 1. Hukkinen et al. described and compared the operative approach and the long-term outcomes of total colon aganglionosis patients in relation to the length of intestinal aganglionosis. They concluded that the outcomes after restorative proctocolectomy for aganglionosis extending up to the mid-small bowel were promising, whereas the long-term outlook in patients with proximal small intestinal disease was dismal without intestinal transplantation [22]. The development of new treatment approaches, including small intestine transplantation, and the clinical introduction of stem cell therapy [23] are expected in the future.

15.8 Conclusions

This study analyzed 4939 HD patients over four decades. The incidence and male-to-female ratio remained stable over time, but the rate of the patients with a family history increased over the past two decades. The combination of a contrast enema and rectal mucosal biopsy with AChE staining will likely become the standard diagnostic tool of HD. TAEPT is now the first choice for the definitive surgical procedure in Japan. However, the locations of the starting line of mucosal dissection varied among cases. We may study the postoperative long-term bowel function with respect to the starting point of mucosal dissection in the future. The overall mortality rate has decreased over time. However, the mortality rate of small intestinal aganglionosis is still relatively high, at 25%. The development of new treatment strategy for small intestinal aganglionosis is called for.

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Conflict of Interest: None.

Appendix

Aichi Children's Health and Medical Center	Aichi
Aichi Prefectural Colony Central Hospital	Aichi
Aso Iizuka Hospital	Fukuoka
Chiba Children's Hospital	Chiba
Chiba University Hospital	Chiba
Department of Gastroenterological Surgery I Hokkaido University Graduate School of Medicine	Hokkaido
Department of Gastrointestinal and Pediatric Surgery, Tokyo Medical University	Tokyo
Department of Surgery, Asahikawa Medical University	Hokkaido
Department of Surgery, Iwate Medical University School of Medicine	Iwate
Department of Surgery, Miyagi Children's Hospital	Miyagi
Department of Surgery, Shiga University of Medical Science	Shiga
Department of Surgery, Tokyo Metropolitan Ohtsuka Hospital	Tokyo
Division of Pediatric Surgery, Integrative Center of Surgery, Gunma University Hospital	Gunma
Dokkyo Medical University Koshigaya Hospital	Saitama
Ehime Prefectural Central Hospital	Ehime
First Department of Surgery, Dokkyo Medical University	Tochigi
Fujita Health University Hospital	Aichi
Fukuoka Children's Hospital	Fukuoka
Fukuoka University	Fukuoka
Fukushima Medical University	Fukushima
Gunma Children's Medical Center	Gunma
Hepato-Biliary-Pancreatic Surgery and Transplantation, Kyoto University Hospital	Kyoto
Hiroshima City Hiroshima Citizens Hospital	Hiroshima
Hiroshima Prefectural Hospital	Hiroshima
Hyogo College of Medicine	Hyogo
Hyogo Prefectural Kobe Children's Hospital	Hyogo
Hyogo Prefectural Tsukaguchi Hospital	Hyogo
Ibaraki Children's Hospital	Ibaraki
International University of Health and Welfare Hospital	Tochigi
Ishii Memorial Aizen-en Aizenbashi Hospital	Osaka
Ishikawa Medical Center for Maternal and Child Health	Ishikawa
Iwate Prefectural Central Hospital	Iwate
Japanese Red Cross Kumamoto Hospital	Kumamoto
Japanese Red Cross Kyoto Daiichi Hospital	Kyoto
Japanese Red Cross Society Fukaya Red Cross Hospital	Saitama
Japanese Red Cross Society Nagaoka Red Cross Hospital	Niigata

Japanese Red Cross Society Sendai Red Cross Hospital	Miyagi
Jichi Medical School	Tochigi
Juntendo University Hospital	Tokyo
Juntendo University Nerima Hospital	Tokyo
Juntendo University Urayasu Hospital	Chiba
Kagawa University Hospital	Kagawa
Kagoshima City Hospital	Kagoshima
Kagoshima University Graduate School of Medical and Dental Sciences	Kagoshima
Kakogawa West City Hospital	Hyogo
Kanagawa Children's Medical Center	Kanagawa
Kanazawa Medical University	Ishikawa
Kansai Medical University Hirakata Hospital	Osaka
Kawaguchi Municipal Medical Center	Saitama
Kawasaki Medical School	Okayama
Kimitsu Chuo Hospital	Chiba
Kitakyushu Municipal Medical Center	Fukuoka
Kitano Hospital	Osaka
Kitasato University Hospital	Kanagawa
Kochi Health Sciences Center	Kochi
Kumamoto City Hospital	Kumamoto
Kumamoto University Hospital	Kumamoto
Kurume University School of Medicine	Fukuoka
Kyorin University School of Medicine	Tokyo
Kyoto Prefectural University of Medicine	Kyoto
Kyushu University Hospital	Fukuoka
Matsudo City Hospital	Chiba
Mie University Faculty of Medicine	Mie
Miyazaki Prefectural Miyazaki Hospital	Miyazaki
Nagano Children's Hospital	Nagano
Nagasaki University Hospital	Nagasaki
Nagoya City University Hospital	Aichi
Nagoya City West Medical Center	Aichi
Naha City Hospital	Okinawa
Nara Hospital Kinki University Faculty of Medicine	Nara
National Center for Child Health and Development	Tokyo
National Hospital Organization Kokura Medical Center	Fukuoka
National Hospital Organization Nagara Medical Center	Gifu
Niigata City General Hospital	Niigata
Niigata University Graduate School of Medicine and Dental Sciences	Niigata
Ohta Nishinouchi Hospital	Fukushima
Oita Prefectural Hospital	Oita
Okayama Medical Center	Okayama
Osaka City General Hospital	Osaka
Osaka Medical Center and Research Institute for Maternal and Child Health	Osaka
Osaka University Hospital	Osaka
Omihachiman Community Medical Center	Shiga
Saga-ken Medical Centre Koseikan	Saga
Saitama Children's Medical Center	Saitama
Saitama City Hospital	Saitama
Saitama Medical Center	Saitama
Saitama Medical University Hospital	Saitama
Second Department of Surgery, Wakayama Medical University	Wakayama
Seirei Hamamatsu General Hospital	Shizuoka
Shimane University Hospital	Shimane
Shizuoka Children's Hospital	Shizuoka
Social Medical Corporation BOKOI Tenshi Hospital	Hokkaido
St. Luke's International Hospital	Tokyo
St. Marianna University Hospital	Kanagawa
St. Marianna University School of Medicine Yokohama City Seibu Hospital	Kanagawa
St. Mary's Hospital	Fukuoka
Takatsuki General Hospital	Osaka
Tohoku University Hospital	Miyagi
Tokai University Hachioji Hospital	Tokyo
Tokai University Hospital	Kanagawa
Tokyo Metropolitan Children's Medical Center	Tokyo
Tokyo Women's Medical University	Tokyo
Tokyo Women's Medical University Yachiyo Medical Center	Tokyo
Tsuchiura Kyodo General Hospital	Ibaraki
University of Tsukuba	Ibaraki
Yamaguchi Prefectural Grand Medical Center	Yamaguchi
Yamanashi Prefectural Central Hospital	Yamanashi
Yodogawa Christian Hospital	Osaka

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Medical Treatment Including Kampo Medicine

16

Minoru Yagi and Suguru Fukahori

16.1 Introduction

Long-term results after radical operations in Hirschsprung's disease (HD) have many kinds of differences in the surgery performed [1–6], the age of treatment, the involved aganglionic segment, the amount of colon resected, and the patient's and parent's perception of fecal continence [7–10]. Functional problems after a pull-through operation, including enterocolitis, constipation, and fecal incontinence, sometimes occur, but the true incidence of each is unclear, and their definitions are various. Understanding the technical differences between the different HD operations is the key to assessing any postoperative problems the patient may experience [11].

16.2 Postoperative Fecal Incontinence and Constipation

Based on our experience, medical treatment including Kampo medicine is shown as below for a child with HD who is not doing well after operative management.

Continence is defined as the ability to have voluntary bowel movements without soiling and without enemas. To achieve this, there must be normal anal canal sensation, voluntary sphincter activity, and appropriate colonic motility [12]. Disruption of any of these factors may result in patients being partially or totally incontinent [13]. Even if the physiological mechanisms needed for continence are intact, surgeons have sometimes found that a child after pull-through operation can still soil. They are not true fecal incontinence and need the appropriate medical therapy to improve soiling [14]. Those with disruptions in their continence mechanism can be termed to have fecal incontinence, as they lack the ability to have voluntary bowel movements.

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Fecal incontinence after radical operation of HD should not occur because patients are born with an anatomically intact continence mechanism, including an intact dentate line and intact voluntary sphincters that surround the anus. All kinds of operative procedures are intended to preserve the anal canal and, therefore, sensation and the sphincter mechanism [14].

A significant change in colonic motility may occur because they involve resection of the rectosigmoid colon as well as varying amounts of more proximal colon. With this loss of the natural fecal reservoir, theoretically, patients should tend to pass stool frequently throughout the day and behave as if their colons manifest hypermotility, but because of an intact dentate line and sphincters, the majority have bowel control [14].

Most patients stool normally or suffer from constipation (hypomotility) after rectosigmoid colon resection, which is not well understood. Problems of soiling after a pull-through involve some disruption in anal canal sensation, sphincter control, and colonic motility. These problems can be investigated and adequate treatments formulated to help get a child clean and dry [14].

If the anal canal and sphincters are intact, it can be concluded that the patient should have the potential for voluntary bowel movements. Such children who also have a large dilated colon on contrast study and a history of constipation exhibit symptoms consistent with hypomotility (atony) and can be treated with a daily stimulant laxative including prokinetic agents like Kampo medicine and probiotics. Besides the above described, a water-soluble fiber is sometimes useful to provide stool bulk, which makes the laxative more effective. Those patients achieving this goal who initially presented with soiling were not retrospectively true incontinent and only had soiling because of overflow incontinence. In case of failure in laxative control, true incontinence may be suspected. These patients may have disrupted anal canal and sphincters or both. In these cases, it is essential to have a daily enema to manage successfully [15].

Children with a nondilated or normal-caliber colon can be considered hypermotile (spastic). Calcium polycarbophil

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and Kampo medicine including Shokentyu-to are suitable to control in Japan. Calcium polycarbophil has been used for treating functional bowel disorder and absorbs liquid in the intestine which swell to form a soft bulky stool as a bulk-producing agent. Levitt et al. recommend loperamide, water-soluble fiber, and dietary modifications in this group of patients [14].

16.3 Evaluation Before Medical Treatment

It is essential to evaluate a patient who is not doing well after surgery for HD before medical treatment. At first, it is important to hear and investigate the concerned postoperative patient about the detailed history including operative records and physical examination focused on the patient's bowel habits (history of constipation, enterocolitis, abdominal distention, failure to thrive, soiling, use of antimotility agents or laxative, need for anal dilations, or colon irrigations) [14]. A contrast enema allows for visualization of the anatomy that exists after the initial operation and gives insight into the motility of the colon and any structural anomalies that may account for the patient's symptoms. This examination discloses whether the colon is dilated or nondilated, and from this image, one can speculate whether the colon manifests hypomotility. This decision-making is key factor to judge the methods of the medical treatment [14].

Levitt et al. reported that disruption of the anal canal's dentate line from a dissection started too low and/or damage to the anal sphincters because of excessive stretching will result in decreased anal sensation and loss of voluntary sphincter control [14, 16, 17].

If a patient has an intact anal canal and sphincters and continues to soil from constipation, despite laxative therapy, a change of the anatomic structure in the colonic pull-through may be the cause of obstruction. These include an obstructing Soave cuff, a stricture, a twisted pull-through, a dilated Duhamel pouch, a very dilated distal segment, or a transition zone pull-through [11], all determined on contrast enema. These can cause obstruction and constipation. These anatomic problems lead to dangerous consequences of stasis, namely, enterocolitis and failure to thrive. In all such cases, a redo of the pull-through is recommended without being deeply attached to medical treatment.

16.4 Medical Treatment

16.4.1 Laxatives Including Enema

Laxatives are not usually prescribed as monotherapy. Enema is a popular method for treating constipation after anorectal surgery in Japan, but laxative function is dependent on several different mechanisms. By distending the rectum, all enemas stimulate the colon to contract and eliminate stool. Other mechanisms, such as those found in phosphate enemas, directly stimulate the muscles of the colon. In addition to glycerin enemas, laxatives are more often described as effective than any other category.

Sodium picosulfate acts as a stimulant laxative by increasing the frequency and the force of peristalsis and promoting electrolyte and water retention in the colon. Sodium picosulfate is most often used as laxatives [18].

Magnesium oxide acts as an osmotic laxative by retaining fluids in the colon to clear the colon and the rectum of their fecal contents [19]. In a nationwide survey in Japan, of 160 adult patients, magnesium oxide was the most commonly used drug [20], but it was used less often than sodium picosulfate in laxatives for pediatric chronic intestinal pseudo-obstruction (CIPO). Sodium picosulfate is a liquid medicine and therefore easy to adjust based on patient condition. For that reason, sodium picosulfate is commonly used in children as laxatives for constipation including after anorectal surgery.

16.4.2 Prokinetics

Prokinetics consist of 5-HT4R agonists, such as cisapride and mosapride, and dopamine antagonists, such as metoclopramide and domperidone, and enhance gastrointestinal motility. Prokinetic drug therapy with agents such as metoclopramide, domperidone, octreotide, and cisapride has had varying degrees of success. Regarding CIPO in pediatric patients, in a national survey of the members of the North American Society of Pediatric Gastroenterology and Nutrition in 1988, 57 of 87 patients were treated with metoclopramide and bethanechol, but these agents provided little or no benefit in promoting motility [21]. The serotoninergic agent cisapride is the only prokinetic agent that has been shown to improve enteral tolerance. Camilleri et al. reported the positive effects of cisapride in accelerating gastric emptying [22] and in improving symptoms in control trials [23], but cisapride is no longer available because of the associated risk of life-threatening cardiac arrhythmias, mainly due to its effect on QT interval. A short-term meta-analysis of randomized controlled trials found that the overall effects of the serotonin agonists appeared to be similar to those of other prokinetics, but mosapride had a higher probability of improving symptoms than other prokinetics such as cisapride in adults with functional dyspepsia [24]. In Japan, mosapride has been used to improve gastric motility. In a nationwide survey in Japan, approximately two-thirds of adult CIPO patients received mosapride [20]. In contrast, Hashizume et al. reported that approximately one-third of pediatric CIPO patients were treated with mosapride [18].

Mosapride is not often used to treat functional dyspepsia in children. In a nationwide survey in Japan, 25% of adult patients used erythromycin for CIPO [20]. Erythromycin is a macrolide antibiotic that exerts specific agonist action on motilin receptors in the stomach and duodenum by inhibiting the binding of motilin to its receptors on gastrointestinal smooth muscle [25]. Emmanuel et al. reported that erythromycin was effective for acute ileus and chronic symptoms in some adult patients (60.0%) with CIPO [26]. Long-term treatment, however, can result in macrolide resistance. From these reports, prokinetics may be an important modality to improve postoperative constipation.

16.4.3 Kampo Medicine

Kampo medicine was used on a daily basis based on the accumulation of the clinical experience. Especially, most of the clinicians in Japan realize the effects of Kampo medicine in pediatric constipation.

Paeoniae radix relieves smooth muscle tonus of the gastrointestinal tracts and is contained in the Keishikasyakuyaku-to, Shokenchu-to, and Keishikashakuyakudaio-to for the treatment of spastic loose stool (hypermotility). Shokenchu-to is a suitable formula for the fragile children with functional abdominal pain including orthostatic dysregulation. This formula contains cinnamon twig, fresh ginger, honey-fried licorice, jujube fruit, malt sugar, and *Paeoniae radix*. It is useful in treating spasmodic abdominal pain including pain related to constipation. Malt sugar sweetens the formula and stops abdominal pain. Cinnamon activates the lymphatic system and dispels "cold," infectious influences. *Paeoniae radix*, as used in this formula, harmonizes the relationship between the energy derived from food and the energy the body uses to protect itself from disease in addition to as above described. Licorice reinforces the ability of malt sugar to stop abdominal pain, while ginger and jujube harmonize the actions of the other warm and sweet herbs.

Juncho-to, Daiokanzo-to, and Choi-joki-to containing powdered *Rhubarb* are used for the treatment of atonic constipation (hypomotility) in addition to the Daikenchu-to. Daiokanzo-to is composed of rhubarb and glycyrrhiza. Choi-joki-to consists of Daiokanzo-to with sodium sulfate. In Japan, Daikenchu-to and Kampo medicine containing powdered *Rhubarb* are commonly used for hypomotile constipation. Daio (powdered *Rhubarb*) contains Sennoside A. Active ingredient is not Sennoside A, but rheinanthrone metabolized with intestinal flora. Daikenchu-to is an exact mixture of powdered ginger root, ginseng, zanthoxylum fruit, and maltose powder as the prebiotic and is traditionally used to treat chronic gastrointestinal disorders or to relieve abdominal pain and distension and adhesive and paralytic ileus for the fragile patients. Daikenchu-to also improves gastrointestinal motility after abdominal digestive surgery [27, 28] and was recently reported to be clinically effective in improving gastrointestinal motility in a case of megacystis microcolon intestinal hypoperistalsis syndrome [29]. Daikenchu-to is suitable for the constipated fragile children with abdominal pain and diarrhea by Kampo medicine containing powdered *Rhubarb*. Daikenchu-to may therefore stimulate intestinal motility and accelerate delayed intestinal transit through the cholinergic pathway and activation of 5-hydroxytryptamine-3 receptor (5-HT3R) and 5-hydroxytryptamine-4 receptor (5-HT4R). The main mechanism of contractile action and improvement of gastrointestinal motility mediated by Daikenchu-to is the release of acetylcholine (ACh) from the cholinergic nerves via 5-HT3R and 5-HT4R stimulation [30–32].

ACh subsequently improves delayed intestinal transit and recovers delayed gastric emptying in postoperative ileus. Daikenchu-to had a favorable clinical effect on severe constipation in fragile children and improved their rectal reservoir function, as seen on anorectal manometry. These effects appeared to be secondary to the stimulation of peristalsis of the intestine, which promoted regular bowel habits [33, 34].

16.4.4 Probiotics

Probiotics are defined as live microbacterial diet supplements that beneficially affect the host by improving intestinal microbial balance [35]. Probiotics were used for the prevention of small bowel bacterial overgrowth, which is a major cause of diarrhea and malnutrition and should be treated with antibiotic therapy. In clinical practice, the most commonly used antibiotics in adults are metronidazole, amoxicillin-clavulanate, doxycycline, and norfloxacine [36], but long-term antibiotic use in pediatric patients risks the development of antibiotic resistance.

On the other hand, it is reported that probiotics (*Lactobacillus casei rhamnosus*, Lcr35) were effective in treating children with chronic constipation [37]. Korterink et al. reported that probiotics were more effective than placebo in the treatment of patients with abdominal pain-related FGID, especially for IBS patients, and sufficient scientific evidence was found for *Lactobacillus* GG [38]. Hashizume et al. reported that *L. casei* was the most frequently prescribed probiotics in the patients with CIPO [18]. On the other hand, it is controversial due to low-quality evidence whether probiotics are more effective than placebo at improving a composite measure of treatment success or defecation frequency in children with constipation [39]. Nevertheless, Kampo medicines were most commonly simultaneously used with probiotics, in the two-treatment combination. Symbiotics consist of probiotics and prebiotics [18]. Most Kampo medicines such as Daikenchu-to contain maltose powder as the prebiotics.

Additionally, probiotics, Kampo medicines, and laxatives were most frequently selected as the three-treatment combination. These combination treatments might have a high synergistic effect in the improvement of gastrointestinal motility compared with Kampo medicines on their own [18]. Other probiotics were prescribed in a similar number of patients. Kanamori et al. reported that probiotic and prebiotic therapy consisting of *B. breve*, *L. casei*, and galacto-oligosaccharides for short bowel syndrome improved the intestinal bacterial flora, inducing the domination of anaerobic bacteria and suppressing pathogenic bacteria, and increased the excretion of short-chain fatty acids in the feces [40]. Short-chain fatty acids have been shown to have several important roles in the intestinal lumen by functioning as an energy source in the intestinal epithelium, increasing intestinal blood flow, and affecting intestinal motility [40]. Wang et al. reported that probiotics significantly diminished the incidence and decreased the severity of Hirschsprung's disease-associated enterocolitis due to decreased pro-inflammatory cytokines, increased anti-inflammatory cytokines, and stable T-lymphocyte levels [41]. Probiotics stabilize the gut mucosal immune barrier and inhibit intestinal inflammation. A meta-analysis of the efficacy of probiotics in irritable bowel syndrome (IBS) found that probiotics reduced pain and symptom severity scores [42]. Probiotics stabilize immune dysregulation in IBS, thereby enhancing the cellular integrity and subsequently protecting the colon and modifying the intestinal microbiota, altering the fermentation pattern inside the colon, and reducing the incidence of flatulence. These previous results demonstrate the beneficial effects of probiotics in IBS compared with placebo [42]. Although few reports have described the clinical efficacy of probiotics with CIPO, probiotics prescribed for CIPO might improve the intestinal bacterial flora and prevent small bowel bacterial overgrowth.

16.4.5 Calcium Polycarbophil

The human stomach presents a mild acidic environment due to the presence of HCl. Polycarbophil absorbs about ten times its own weight of water under acidic conditions, but the swelling ratio markedly increases at above pH 4.0 and reaches 70 times the initial weight under pH-neutral conditions. In an acidic condition of the stomach, calcium polycarbophil is excellent in the disintegration and sufficiently exhibiting actions such as the adjustment of intestinal water content. It is used as stool stabilizer to treat constipation, diarrhea, and abdominal discomfort. Bulk laxatives absorb liquid in the intestines and swell to form a soft bulky stool. The bulky mass stimulates the intestinal muscles, speeding stool transit time through the colon. Results usually occur within 12–72 h. Calcium polycarbophil will not work without increased fluid intake. Chiba et al. reported that calcium polycarbophil was useful in improving colonic transit, bowel movements, stool form, and abdominal pain in both types of IBS, and improvement in colonic transit relieved abdominal pain in IBS patients [43].

16.5 Conclusions

The attending surgeons should perform careful assessment and diagnostic plan and are able to improve the quality of life of many of the patients with HD who are not doing well after operations. Bowel management, medications, and/or redo operations all should be taken into consideration. However, it is no exaggeration to say that it is the excellent performance of the primary operation that has the best opportunity to provide these patients with the ideal outcome.

The literature is unclear concerning which operative procedure for HD provides the best results in bowel control, and it seems that there is no relationship between the incidence of fecal incontinence and the type of initial procedure [44], but certainly this is an important problem in a significant number of cases [45]. Levitt et al. reported that the transanal pull-through is a great maneuver, but it is uncertain that this operation may be leading to a tendency to start the dissection too low and may be causing too much stretching by retractors to gain visualization that can damage the anal canal [14].

In assessing the soiling postoperative patient with HD, it is important to discuss whether the colon of the patient is spastic or dilated. A surgical technique that fails to preserve the dentate line or overstretches the sphincters may be a contributing factor in incontinence in these patients [14]. Examination under anesthesia to determine the integrity of the anal canal and status of the sphincters is important and adjusts the patient's expectations concerning long-term functional result and helps determine what kinds of medical treatment including enema are administrated. In case of giving laxatives, the dosage must be determined on an individual basis. As the result, it is important to discuss the etiology of pathophysiology and postoperative fecal incontinence despite the existence of normal ganglion cells and to determine whether the type of the incontinence originated from hypermotility or hypomotility. In case of anal canal and sphincters intact with hypomotility (atonic constipation), it is necessary to administrate laxatives including prokinetics and Kampo medicine (Juncho-to, Daiokanzo-to, Choi-joki-to containing powdered *Rhubarb*) as constipation in addition to probiotics. In another case of anal canal and sphincters intact with hypermotility (spastic frequent loose stool), it is suitable to administrate calcium polycarbophil and Kampo medicine Shokentyu-to including *Paeoniae radix* in addition to probiotics. Probiotics stabilize the gut mucosal immune barrier and inhibit intestinal inflammation even in any type.

Successful management depends on the appropriate evaluation and medical treatment and leads to clean and dry around the neo-anorectal lesion.

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Swenson's Procedure

17

Eiji Nishijima

The classic approach to the neonate and infant diagnosed with Hirschsprung's disease (HD) had been to create a diverting colostomy and to wait until 6–12 months of age to perform the definitive pull-through [1–5]. This approach has changed considerably over the past four decades and has been predominantly changed to primary repair without colostomy. The use of laparoscopy to facilitate both the leveling biopsy and the pull-through procedure has also become common. The transanal approach is now used by a large proportion of pediatric surgeons using Soave's or Swenson's technique [6–14].

Swenson's procedure consists of three principles: (1) complete removal of the aganglionic segment, (2) an oblique anastomosis proximal to the dentate line to preserve anal sphincter functions, and (3) an extra-pelvic anastomosis. The dentate line is a key landmark for Swenson's pull-through procedure in order to preserve fecal continence and facilitate voluntary bowel movement. The surgeon should decide a resection line in the anorectum based on the dentate line. Swenson described the proper oblique line of resection that is 0.5–1.0 cm apart from the dentate line on the posterior midline and 2.0 cm above the dentate line anteriorly. Many surgeons now understand that this resection means the resection of the proximal two third of the internal sphincter muscle posteriorly, which is aganglionic in HD. The residual one third of the aganglionic internal sphincter muscle keeps the denervated muscle tonus and plays an important role of keeping nocturnal continence.

The author learned Swenson's procedure from Dr. Kimura, K. (Kobe) who had learned this from Dr. Fisher, J.H. (Boston). From a standpoint of a surgeon located at the periphery of Swenson's pedigree, the author will review progress of surgical techniques in Swenson's procedure for these four decades and emphasize importance of adjustment to the resection level of the internal sphincter according to the various levels of the pull-through bowel.

17.1 Status Quo of Surgical Treatment Using Swenson's Procedure

17.1.1 Swenson's Procedure with Laparotomy (Transabdominal Swenson)

The original laparotomy procedure was introduced by Dr. Orvar Swenson in 1948 [1]. He first detected the narrow segment in the most distal colon as a cause of the bowel obstruction and described aganglionosis as the cause of HD in 1949 [2]. He also described the first successful surgical treatment which consisted of three main concepts: (1) complete removal of the aganglionic segment including the muscle layer, (2) preservation of anal sensation and anal sphincter function leaving a part of the intact transitional epithelium and a part of internal sphincter muscle using oblique anastomosis proximal to the dentate line, and (3) an extra-pelvic anastomosis between the everted or prolapsed aganglionic anorectum and the pulled-through ganglionic bowel [1–7]. The dentate line was selected as a key landmark for the Swenson's pull-through procedure in order to decide the anorectal resection line and the anastomotic line for preservation of fecal continence and promotion of voluntary bowel movement.

17.1.1.1 Complete Removal of the Aganglionic Segment [7–11]

The patient is positioned on the operating table to provide simultaneous exposure of the perineum and abdomen. The rectum is washed out and dilated with Hegar dilators or a finger before beginning the pull-through surgery under general anesthesia. After the usual preparation, a small Silastic Foley catheter is inserted into the bladder for decompression during the operation and continued to place for the first 5 postoperative days to secure the urinary flow. A left

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paramedian incision is advantageous because the splenic flexure can be more easily mobilized. Once the abdomen is opened, the sigmoid colon or descending colon can be delivered into the wound. First it is necessary to confirm the most distal part of the normal bowel containing normal ganglion cells which is revealed by serial frozen sections. The normal portion of the bowel is divided with a stapling device above the transition zone. Some sigmoidal arteries should be divided to provide a length of ganglionic bowel sufficient to reach the peritoneum. The marginal vessels must be preserved to maintain blood supply at the anastomotic site. If necessary, the splenic flexure should be also mobilized in order to provide adequate length of ganglionic bowel. When the lesion is over the transverse colon, it is necessary to divide the middle colic artery so that the right colon connected with the right colic vessels may be turned down to the perineum using counterclockwise rotation.

The pelvic dissection is started by incising the peritoneal reflection over the rectum. The vas deferens, prostate, seminal vesicles, urethra, uterine appendages, vagina, and ureters are at first identified in the course of the peritoneal incision and the pelvic dissection. Then the operating surgeon starts dissecting the rectum caudally. This is a critical part of Swenson's procedure. The entire subsequent dissection is kept immediately on the surface of the muscular wall of the rectum. Swenson himself emphasized a definite effort to start dissecting through the surrounding fatty tissue until the muscle fibers of the bowel are identified. If the dissection is performed outside or apart from this plane, one may damage the genitourinary innervation. All the rectal dissection through the pelvis is kept immediately on the bowel wall by separating tissue with the scissors or a pure-cut mode of electrocautery to identify the blood vessels entering the bowel wall. Each vessel should be clamped with a hemostat and divided. These vessels may be coagulated on the bowel side and should be ligated with fine absorbable sutures on the pelvic side to prevent burning to the surrounding tissue. These tedious dissections can be facilitated by the assistant applying upward traction both on the end of the aganglionic rectum and on the deep part of the bladder wall with externally placed stay sutures. The anterior dissection should be performed about 2.0 cm distal to the peritoneal reflection. The posterior dissection should be performed until reaching to the anal verge.

17.1.1.2 Preservation of Fecal Continent Function [1–7, 11]

Anal sensation and anal sphincter function can be left adequately by leaving both a part of the undamaged transitional epithelium and a part of internal sphincter muscle. The anterior rectal wall is dissected toward the anal verge about 2.0 cm from the dentate line, while the posterior wall is dissected to 0.5–1.0 cm from the dentate line in order to avoid too much resection of the internal sphincter muscle. The extent of the rectal dissection is estimated by putting the index finger into the depths of the rectal dissection plane posteriorly, while the surgeon examines the rectum and palpates the index finger from the perineum. The surgeon can accurately judge the extent of the dissection only when the rectum has been prolapsed through the anus and the dentate line has been directly observed. The rectal stump is everted using a long clamp through the anal canal and grasping the inside of the closed rectal stump. The sufficient dissection is showed with easy exposure of the dentate line at the posterior midline. The distal rectal dissection must be precise, because there will be a recurrence of obstructive symptoms in case of insufficient rectal resection especially on the posterior midline.

17.1.1.3 Extra-Pelvic Anastomosis Between the Aganglionic Anorectum Prolapsed and the Pulled-Through Ganglionic Bowel [1–7]

The symmetrical four points of the planned cutting end of the anorectal wall are pulled out with traction sutures evenly placed on the mucosa in order to prevent retraction of the cut edge. The anterior half of the everted anorectal wall is cut 2.0 cm proximal from the dentate line. Then the posterior wall will be no longer than 0.5–1.0 cm in length when cut the posterior half of the everted rectal wall. A long clamp is inserted through this anterior opening to grasp the sutures placed through the closed end of the proximal colon. The ganglionic colon is pulled through the opening of the everted rectum with the sutures without twisting. The mesenteric border of the proximal ganglionic colon must extend 2 cm beyond the rectal incision without tension and with adequate blood supply.

Interrupted 5–0 absorbable sutures are placed through the cut muscular edge of the rectum and the seromuscular layer of the pull-through colon. Placing and pulling the traction sutures can expose the anastomotic sites clearly and prevent retraction of the anorectal stump during the anastomosis. The amputation of the rectum is completed after the sutures have been completed on the anterior half. The surgeon obliquely cut the posterior half of the everted rectum within 0.5–1.0 cm from the dentate line at the posterior midline. Next mucosal (near full thickness) end-to-end anastomosis is performed with absorbable 4–0 sutures interruptedly. During the anastomosis of the posterior half, the Trendelenburg position improves the exposure of the posterior anastomotic site. Because the circumference of the proximal colon is often larger than that of the distal everted anorectal stump, care must be taken not to fold in a portion of the proximal colon and thereby not to leave excessive space between sutures. The additional sutures should be placed at the excessive spaces to compensate for the discrepancy. It is helpful to

keep sutures at each quadrant for outward traction to accurate anastomosis. When all of the full-thickness sutures are placed, the anastomosed anorectum is retracted back into the pelvis immediately after cutting all sutures.

Then the surgeons move to the abdominal field after changing gloves, and the pelvic peritoneum and the abdominal incision are closed with clean instruments.

17.1.2 Primary Swenson's Procedure Without Colostomy (Primary Transabdominal Swenson) [15–18]

Swenson performed his procedure without colostomy and described it in his first report in 1948 in spite of poor condition for the primary anastomosis [1]. However, Swenson himself recommended the creation of diverting colostomy first and then the definitive procedure after complete recovery of the patient's general condition. In 1980, the primary pull-through with Soave's procedure without stoma was intentionally introduced to avoid the child with colostomy being neglected at home [15]. With the patient's conditions improving and the surgical techniques also improving in the 1980s, the primary pull-through including Swenson and Duhamel's procedures trends in many institutions all over the world to avoid stomas. A staged approach should be preserved in the situations specifically for poor patient's conditions and in case of inadequate pathological setting for the ganglion study in frozen sections [13, 14].

17.1.3 Swenson's Procedure Using Laparoscopic Techniques (Laparoscopic Swenson) [19–21]

Georgeson et al. first described the laparoscopic approach for HD using Soave's procedure in 1995 [18]. He recommends that the biopsy is initially performed to identify the transition zone and the rectum is mobilized below the peritoneal reflection using laparoscopic approach [18]. The short mucosal dissection is also performed through a perineal transanal approach. The rectum is then prolapsed through the anus. The anastomosis between the everted anorectum and the pull-through colon is performed from below or perineum. Curran and Raffensperger described the laparoscopic Swenson's pull-through in 1996 [20]. The laparoscopy-assisted rectal dissection can be performed in the same fashion as with the laparotomy approach. The most important technical point is dissecting the rectum just on the muscular surface without being apart from the correct plane using the energy devices with minimal energy. The successful laparoscopic Swenson resulted in reduced morbidity [20].

As for a robotic-assisted Swenson's procedure, the surgeon who is familiar with the laparoscopy-assisted Swenson's procedure can use this robotic-assisted technique during the meticulous rectal dissection theoretically easily [22].

17.1.4 Swenson-Like Approach Using Transanal Dissection (Transanal Swenson)

The transanal pull-through using Soave's endorectal procedure was first described by De la Torre and Langer for the patients with a clear transition zone in the rectosigmoid region on the contrast enema [23]. This was really an epoch-making approach for HD. Lots of the transanal pull-through trials were reported and showed generally good results from the different institutions [23–28]. However, one of the postoperative obstructive factors is still a long residual muscle cuff leaved in the anal canal, which is derived from the essence of the endorectal pull-through [27]. Accordingly, the cuff length tends to be shorter and shorter to 1.0 cm in the most distal part of the rectum in Soave's procedure [27, 28].

The transanal full-thickness dissection of the rectum was reported in 2003, performing in the prone or lithotomy position [29–32]. When a laparoscopic or umbilical laparotomy biopsy and mobilization is planned, the dissection is performed in the lithotomy position to avoid intraoperative conversion of the position. By placing a Lone Star retractor (Cooper Surgical) at the anocutaneous junction, the dentate line can be clearly detectable. Before starting the placement of the traction sutures, these hooks should be replaced in the proximal rectal mucosa 0.5 cm apart from the dentate line so as to protect the transitional epithelium adjoining to the dentate line [31]. After placing the circumferential traction sutures in the rectal mucosa 1.5 cm posteriorly and 2.5 cm anteriorly apart from the dentate line, a full-thickness circumferential incision 1.0 cm posteriorly and 2.0 cm anteriorly above the dentate line is made obliquely using mainly a pure-cut mode of electric cautery with the lowest energy using a needle-point knife. The surgeon should continue the dissection just on the rectal wall with a meticulous technique in the proper plane, dividing vessels at the point where they enter the rectum. The rectal dissection is easier on the anterior surface (a urethral or vaginal side) of the rectum than posterior because of poor vascularity. Care must be taken to keep the dissection on the rectal wall. When the peritoneum is opened, the sigmoid and more proximal bowel can be pulled out as dividing the entering vessels with the posterior or mesenteric dissection. If necessary, frozen sections are sent to the pathology laboratory. The two-layered anastomosis between the anorectum in situ and the pull-through segment of the normal bowel is performed in the anal canal without difficulty by the use of the Lone Star retractor, not

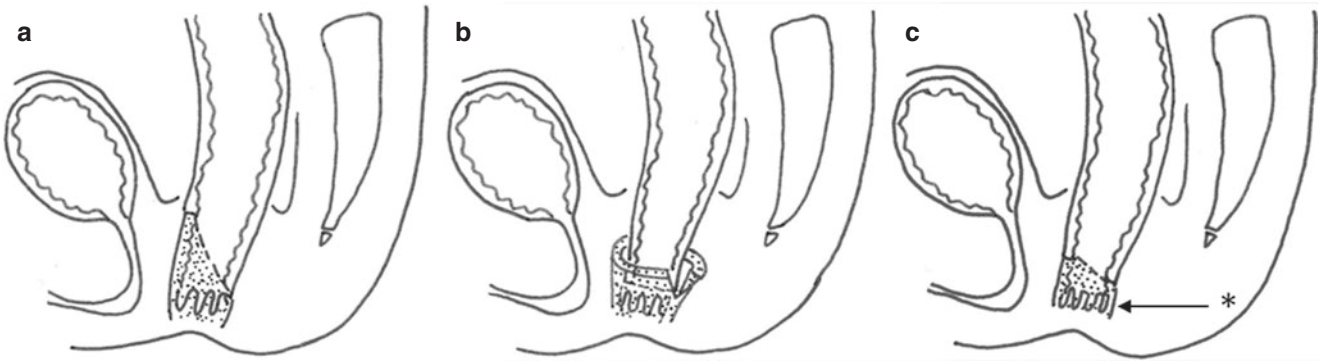

Fig. 17.1 Recent modification of Swenson's procedures. (**a**) Modified transabdominal Swenson's pull-through consisted of minimal dissection of the anterior side of the rectum resulting in strongly oblique anastomosis. (**b**) Transanal "Soaveson's" pull-through with 1 cm muscle cuff incised posteriorly 0.5 cm above the dentate line. (**c**) Transanal Swenson-like pull-through anastomosed to 1.5 cm anteriorly and 0.5 cm posteriorly from the dentate line (dotted areas, aganglionic segments; dotted lines, anastomotic lines; wavy lines, dentate lines)

using the eversion technique originated from Swenson. At this point it can be called the Swenson-like anastomosis [31]. If the full-thickness dissection is emphasized, this procedure can be called as the transanal Swenson's procedure. The Lone Star hooks should be replaced at the anocutaneous junction prior to making the full-thickness anastomosis. A two-layered anastomosis consists of suturing the seromuscular layers and the mucosal (or near full-thickness) layers. The seromuscular layer of the pull-through segment is anastomosed to the outer muscular edge of the incised anorectal wall. The full-thickness edge of the pull-through colon is anastomosed to the muscular and mucosal edge of the incised anorectal wall. A one-layer anastomosis may be effective to avoid formation of anastomotic stricture [33]. The full-thickness edge of the pull-through colon is simply anastomosed to the full-thickness edge of the incised distal anorectal wall.

As described earlier, the muscular cuff has been created shorter and shorter, and a 1 cm cuff is left in order to prevent cuff-related stenosis in transanal Soave's procedures. This short-cuff method is now sometimes referred to a "Soaveson's" procedure because it is approaching a full-thickness resection same as Swenson's procedure (Fig. 17.1b) [14, 34]. The surgeon should care to avoid overstretching from retraction during the rectal dissection. Finding and keeping the perfect full-thickness plane is essential to a safe dissection for the Swenson and "Soaveson" approaches.

17.1.5 Modifications in Swenson's Procedures

Many surgeons tried to reduce the difficulty and tedium of the Swenson's rectal dissection. The author also tried to reduce the area of the anterior dissection leaving the distal anterior rectal wall attaching to the bladder neck, prostate, and urethra in male or vagina in female. The posterior and lateral sides are dissected deeper to the anal verge with lots of ligations and/or applying bipolar electrocautery. On the other hand, the internal sphincter muscle is incised at 0.5–1.0 cm apart from the dentate line on the posterior midline during the anastomosis under the strong traction of the inverted anorectal wall [33]. The anastomosis becomes more oblique, and this oblique anastomosis facilitates both to overcome a large difference of the anastomotic apertures and to prevent an anastomotic stricture shown as Fig. 17.1a. A lower abdominal skin crease incision combined with a left paramedian muscle splitting laparotomy is also useful to expose the rectosigmoid, descending colon, and splenic flexure, leaving a good cosmetic result.

17.2 Future Prospects of Surgical Treatment Using Swenson's Procedure

17.2.1 The Originality of Swenson's Procedure [11]

The most important originality of Swenson's procedure is a full-thickness rectal resection. This is the only procedure that leaves behind essentially no aganglionic bowel component. In other words, this is a theoretically correct procedure, instead of a technically difficult one. Swenson's procedure will last in the future as a definitive surgery for HD because of this theoretical correctness and wide availability to specific conditions such as for the redo surgery and for pull-through with the patched colon segment. The surgeon can control the residual amount of the sphincter muscle by adjusting the incision level of the anorectum at the posterior midline during the definite anastomosis. It is simple and technically easy to decide the posterior incision level in this procedure. When the normal colon is anastomosed to the anus, this can propel the stool against the mod-

erate amount of aganglionic internal sphincter muscle with voluntary straining. When the normal ileum or ileum with patched aganglionic colon is anastomosed to the anus, this ileum can't propel the stool against the too much residual internal sphincter muscle with voluntary straining. It is the surgeon's work to decide where or how much internal sphincter should be incised. The incision level on the posterior midline should be 0, 0.5, and 1.0 cm from the dentate line in case of ileum with patched colon, ileum, and colon, respectively [35–37].

Using Swenson's procedure for HD, the surgeon can perform the definitive surgical repair consisted of entire removal of aganglionic bowel, pulling though ganglionic bowel and preserving the anal canal and sphincter mechanism.

17.2.2 Extensive Aganglionosis and Near-Total Intestinal Aganglionosis

Kimura's patch procedure of the right colon is indicated for the patients with excessive loss of water and electrolytes via ileostomy/jejunostomy in extensive aganglionosis [35–37]. The colonic patch graft works well to reduce the amount of stool via ileostomy converting semi-formed stool and promotes enteral feeding which leads to weaning from the parenteral nutrition. At the pull-through surgery, the most distal part of the side-to-side ileocolostomy segment, instead of the ileal segment attached distal to the ileocolostomy segment as in Fig. 17.2, should be pulled down and should directly anastomose to the anus. If the most distal part of the side-to-side ileocolostomy segment is pulled down to the anus, this does not cause too much stasis and does work to increase absorption of water and electrolytes. With this arrangement of the side-to-side ileocolostomy, peristalsis does not close the widened lumen, and there is no effective forward movement of the bolus. However, the side-to-side ileocolostomy segment is efficiently compressed with the patient's sufficient straining power during the bowel movement. It is also important to incise the internal sphincter muscle just on the dentate line on the posterior midline. The anal tonus should be decreased because the bowel peristalsis of the ileocolostomy segment only is not enough to evacuate the stool. The patient needs to strain to pass the stool against the residual aganglionic internal sphincter.

If Ziegler's myectomy-myotomy procedure for near-total intestinal aganglionosis works well to increase absorption from the elongated jejunoileal myectomy-myotomy segment, this segment can also be pulled down to the anus using Swenson's technique with fecal continence and voluntary bowel movement from my personal experience [35–37].

17.2.3 Swenson's Procedure as Redo Surgery [38–44]

The three typical procedures, Swenson's, Soave's, and Duhamel's, are available to perform redo pull-through procedures [13, 14, 38–44]. Pena et al. applied a posterior sagittal anorectoplasty as a redo operation for the patients with severe scarring and fibrosis of the pelvis or a stricture or fistula not easily accessible through peritoneum or a transanal route [39, 42]. Operative indications of redo surgery for the patients after definitive surgery are a stricture or kinking, a dilated pouch, an obstructing Soave cuff, a residual aganglionic segment, a transition zone bowel pulled through, and/or recurrent pelvic abscesses or fistulas [42–44]. Levitt and Pena et al. reported excellent management for defecation and surgical techniques using Swenson's full-thickness resection through an anal canal and peritoneal cavity in redo surgery for HD [38–40, 42–44].

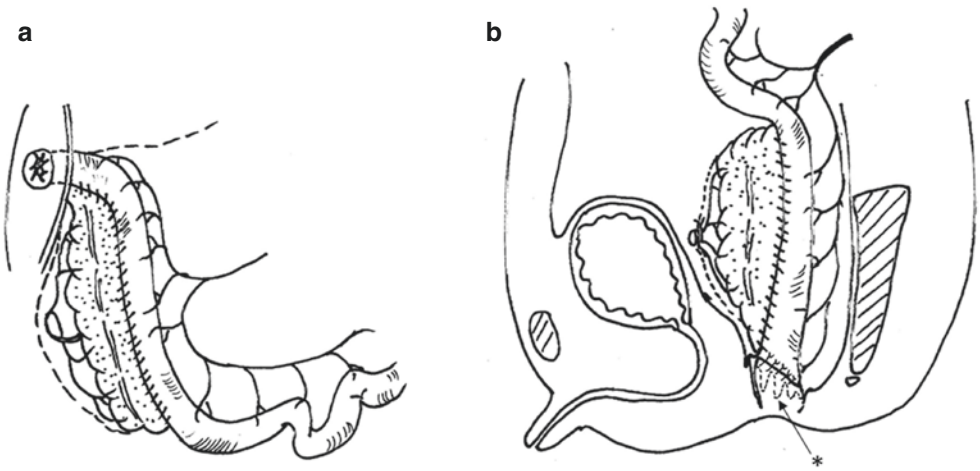

Fig. 17.2 Kimura's colonic patch procedure. (**a**) A ileostomy with side-to-side ileocolostomy segment. The segment directly attached to the abdominal wall. (**b**) A pull-through procedure using the abdominal Swenson's technique. The mesocolon is incised to bring the segment to the anus. The posterior internal sphincter is incised just on the dentate line to weaken the denervated muscle tonus. (dotted areas: aganglionic segments, dotted lines: anastomotic lines, a wavy line *: the dentate line)

The most important Swenson's principle is removal of the entire obstructive segment of the distal bowel. The author believes that this principle will survive in the future adding various points of technical innovation such as a transanal approach especially resecting full thickness of the aganglionic anorectum. Based on the long-term studies on the outcomes such as fecal continence, sexual activity, and psychosomatic development after surgical treatment, a more personalized approach including the different selection of the posterior incision level of the sphincter muscle, such as 0.0, 0.5, and 1.0 cm above the dentate line, will become acceptable to the specific form of the disease including total colon HD and near-total intestinal HD. The pediatric surgeons must continue to learn and develop the new techniques in the proper training system.

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Laparoscopic Modified Duhamel Procedure

18

Naoto Urushihara

The Duhamel operation [1] is one of the most widely performed operations for Hirschsprung's disease (HD). The original Duhamel procedure has the benefit of less pelvic dissection and less anastomotic stricture, but fecalomas resulting from a blind rectal pouch are the most common postoperative complications. The Z-shaped colorectal side-to-side anastomosis was introduced by Ikeda [2] in 1967 to improve the Duhamel procedure, and it eliminates the blind rectal pouch. This procedure provided excellent long-term results [3]. Several laparoscopic Duhamel-type procedures for HD have been reported [4–8], with the advantages of less pain, improved cosmesis, and faster recovery than with open surgery. In our department, a Z-shaped anastomosis using a linear stapling device has been used as the treatment of choice for HD for a long time, providing satisfactory long-term results [9]. A laparoscopic approach was adopted to perform this Z-shaped anastomosis in 2001 [8]. Our laparoscopic modified Duhamel procedure is presented, along with some technical points.

18.1 Preoperative Care

Patients are admitted 2 days prior to surgery and undergo saline colonic irrigation pre- and intraoperatively. All patients are fasted on the day before surgery. An oral polyethylene glycol solution is given to older children. Patients receive preoperative intravenous antibiotics that are continued for 3 days postoperatively.

18.2 Surgical Technique

18.2.1 Patient Position and Port Placement (Fig. 18.1)

Under general and sacral anesthesia, younger patients are placed in a supine position with the pelvis elevated at the edge of the operating table, while older children are placed in the lithotomy position. Before the procedure, rectal irrigation is carried out on the operating table. A nasogastric tube is placed, and a urinary catheter is inserted after induction of anesthesia.The operation is performed by two operators: one for the laparoscopic part and the other for the perineal part. The operation is carried out using three ports. A 5-mm trocar is initially inserted through an intraumbilical incision using an open technique, and pneumoperitoneum of 8–12 mmHg is established. Two additional ports are placed under direct vision: a 5-mm right subcostal port for a 30° 5-mm telescope and a 5-mm port to the right lower quadrant for 3- and 5-mm instruments.

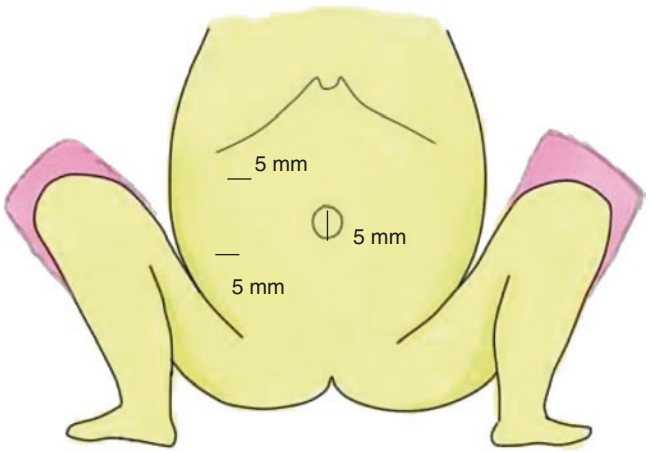

Fig. 18.1 Patient position and port placement

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18.2.2 Biopsy and Colon Dissection

The procedure is started by taking biopsies of the colon. The transition zone is identified first, and a seromuscular frozen biopsy is taken from the colon 3 cm above the transition zone to confirm the presence of ganglion cells. The biopsy sites are sutured using 4-0 vicryl to readily identify the normoganglionic bowel at the time of the excision of the aganglionic bowel. The sigmoid mesentery is mobilized, and the dissection is moved to the patient's left side, while taking care of both ureters and the deferent ducts in males. The marginal artery of the colon is carefully preserved to maintain the blood supply to the colon (Fig. 18.2a). The superior rectal artery is divided using ultrasonic shears or hemoclips. When necessary, the left colic artery or inferior mesenteric artery is divided. Anterior dissection of the rectum is not carried out. Dissection of the rectal posterior wall is carried downward to the level of the levator ani muscle (Fig. 18.2b). At the time, care must be taken to preserve both hypogastric nerves. When the aganglionosis extends higher, the mobilization needs to extend to the splenic flexure and beyond.

18.2.3 Anal-Side Operation and Colon Pull-Through

After adequate dissection of the sigmoid colon and proximal retrorectal, the anal-side operation is started by the other surgeon. A Lone Star retractor is used to expose the anus. A transverse incision is made using electrocautery on the posterior rectal wall at the level of the dentate line

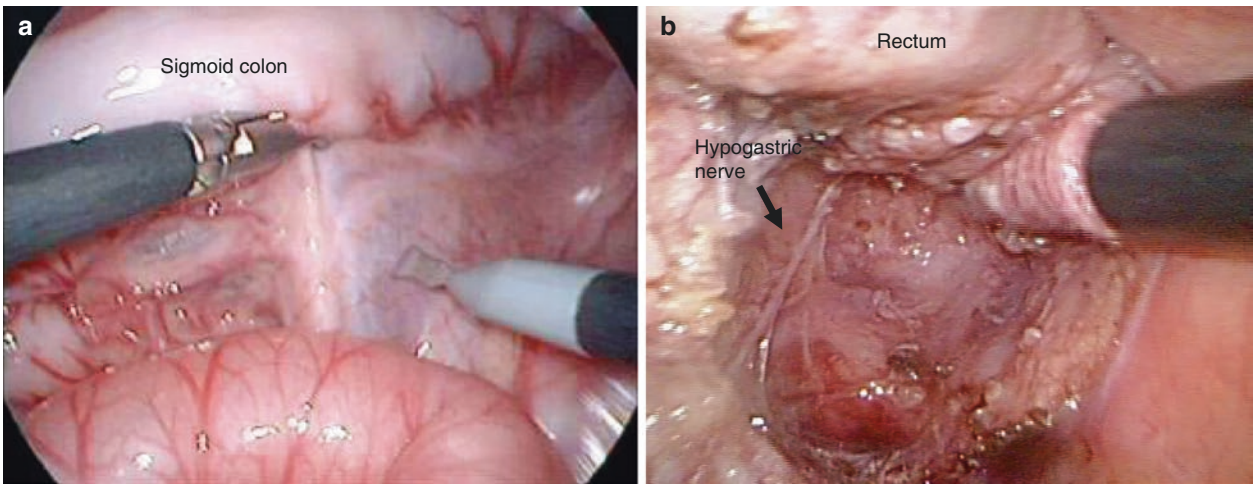

Fig. 18.2 (**a**) Dissection of the sigmoid colon. (**b**) Dissection of the retrorectal

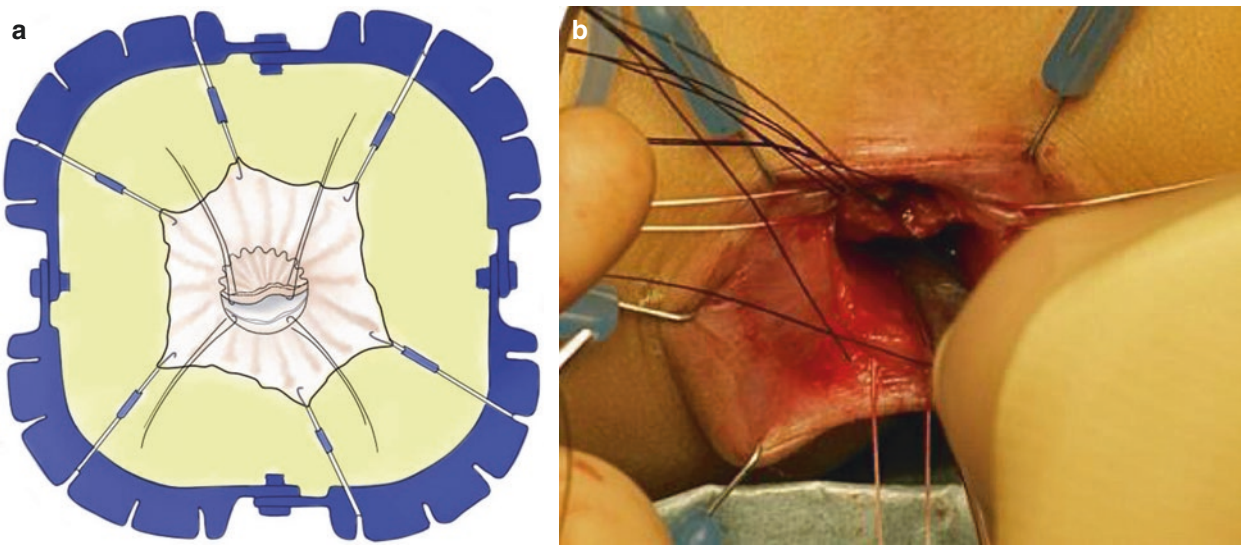

Fig. 18.3 (**a**) Lone Star retractor for exposing the anus. (**b**) Transverse incision on the posterior rectal wall at the level of the dentate line and full-thickness retrorectal dissection

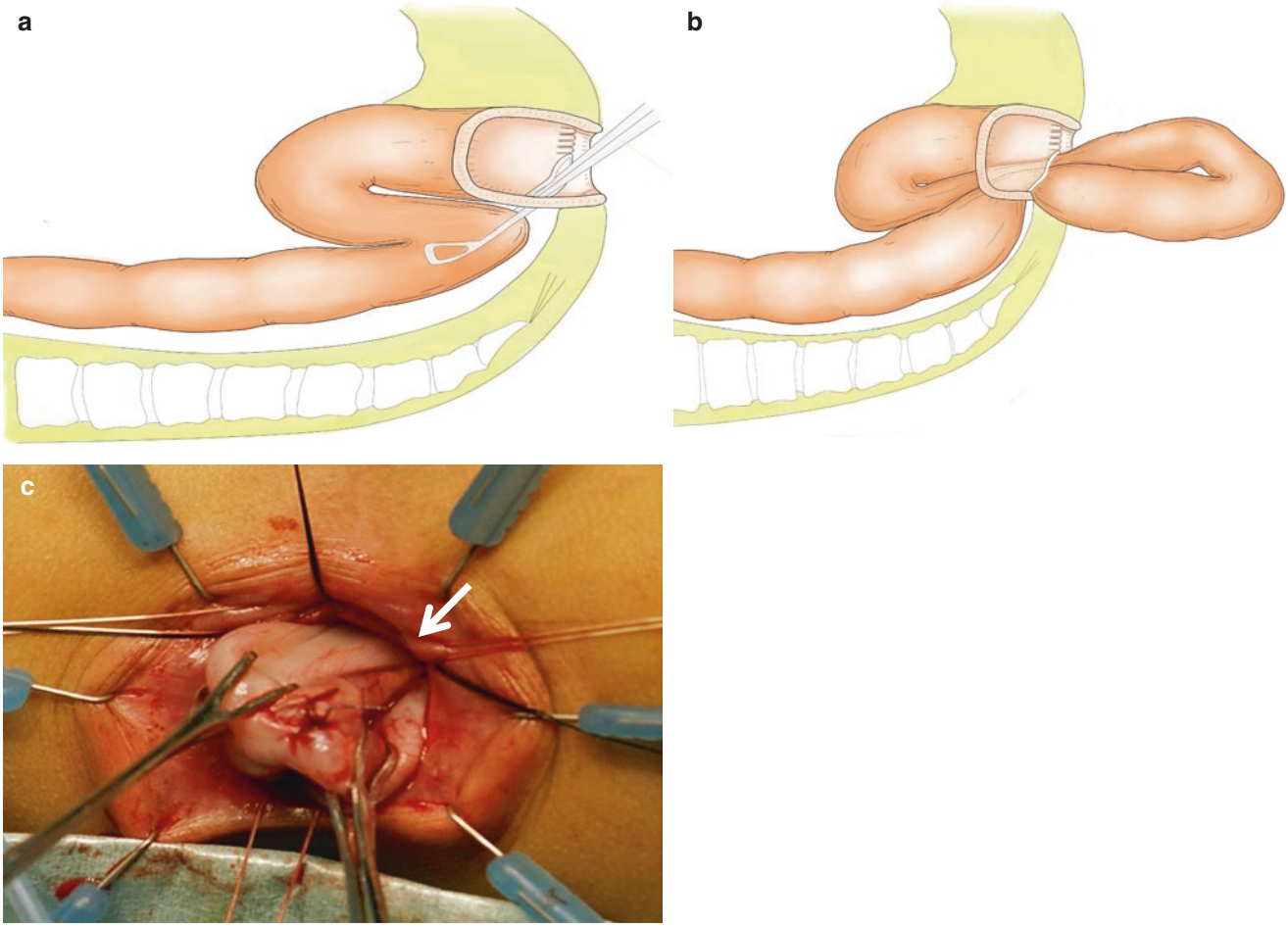

Fig. 18.4 (**a**, **b**) The dissected proximal colon is grasped using tissue-grasping forceps through the incision in the posterior rectum and pulled down through the presacral space. (**b**) External view of the pulled-down colon

(Fig. 18.3a). Several stay sutures are placed at the cut end of the rectum to readily perform the colorectal anastomosis. A retrorectal dissection is performed using Kelly forceps or a finger (Fig. 18.3b). The full-thickness dissection is extended upward, and then a retrorectal tunnel between the anal side and the peritoneal cavity is completed. Next, the dissected proximal colon is grasped using tissue-grasping forceps introduced through the incision in the posterior rectum and pulled down through the presacral space (Fig. 18.4). The colon is extracorporeally divided using the Endo GIA as distal as possible (Fig. 18.5), and the everted rectum is then returned to the abdomen (Fig. 18.6a). After confirming laparoscopically that the distal colon is positioned straight without twisting and lies with the antimesenteric side facing anteriorly, the excess bowel is resected above the previous biopsy site. Next, we perform saline irrigation of the colon and rectum to prevent fecal contamination.

18.2.4 Z-Shaped Anastomosis Without a Blind Rectal Pouch

The rectal stump, which has been returned to the abdomen, is resected approximately 1 cm above the peritoneal reflection from the laparoscopic approach, and the resected rectum is then removed via the anus (Fig. 18.6b, c). A transverse incision is made on the anterior wall of the ganglionic colon at the level of the proximal rectal end (Fig. 18.7a). The posterior wall of the upper rectum and lower edge of the incised anterior wall of the colon are then anastomosed by interrupted sutures (Fig. 18.7b).

From the anal-side approach, anastomosis of the incised posterior wall of the rectum and the pulled-down colon is performed in a single layer using interrupted sutures of 4-0 vicryl (Fig. 18.8a). Under laparoscopic view, the Endo GIA 60 is inserted through the anus to divide the posterior rectal wall and anterior colonic wall (Fig. 18.8b, c). Usually, two

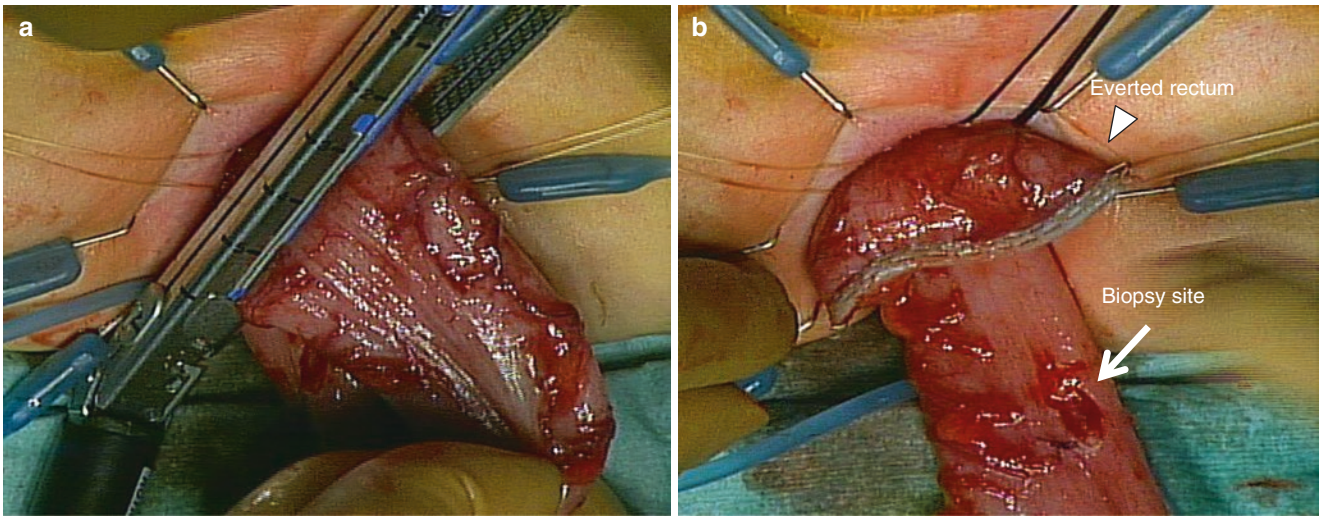

Fig. 18.5 (**a**) The colon is divided using Endo GIA. (**b**) Biopsy site (arrow). Everted rectum (arrow head)

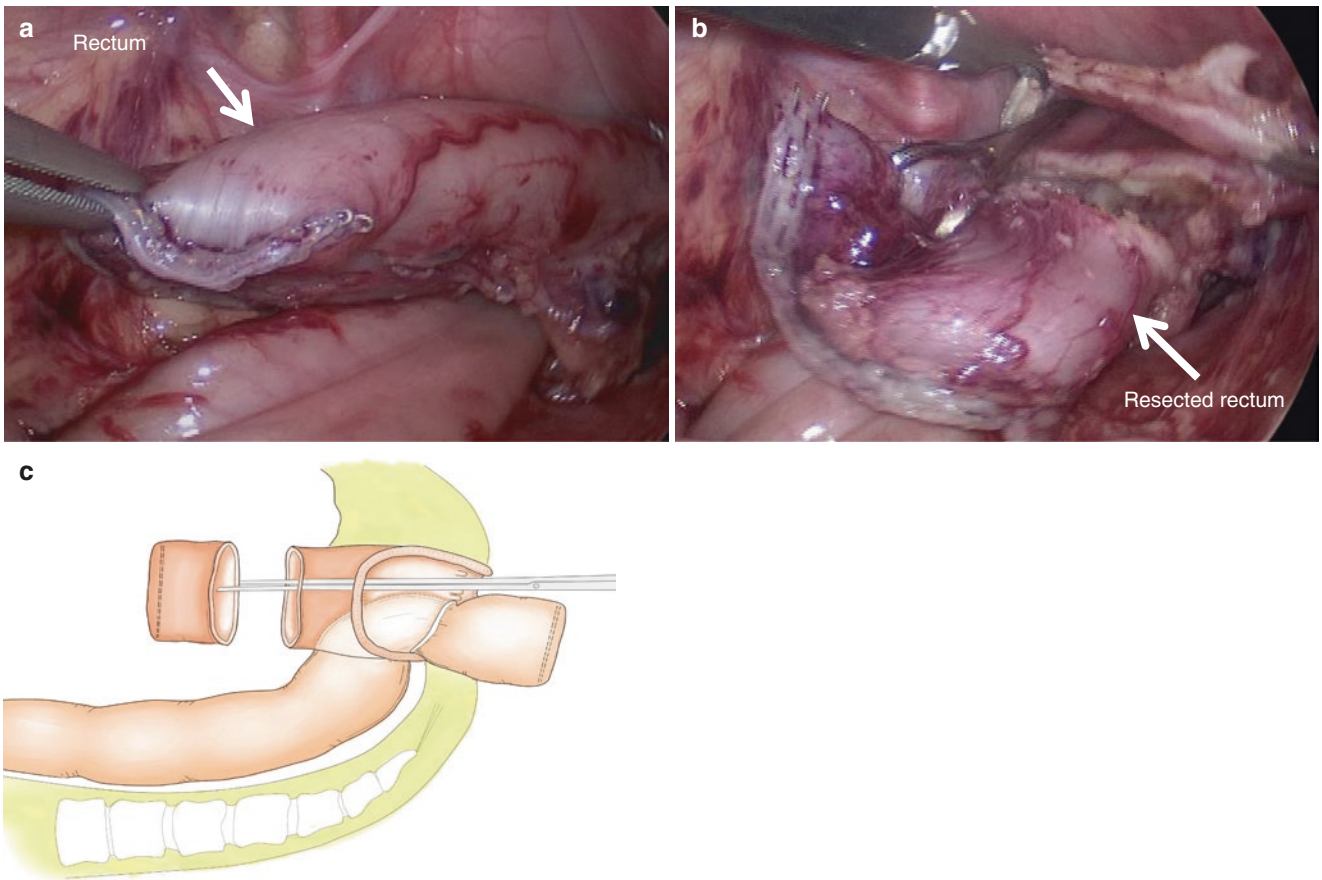

Fig. 18.6 (**a**) The everted rectum is returned to the abdomen. (**b**, **c**) The rectal stump is resected 1 cm above the peritoneal reflection, and the resected rectum is removed via the anus (arrow)

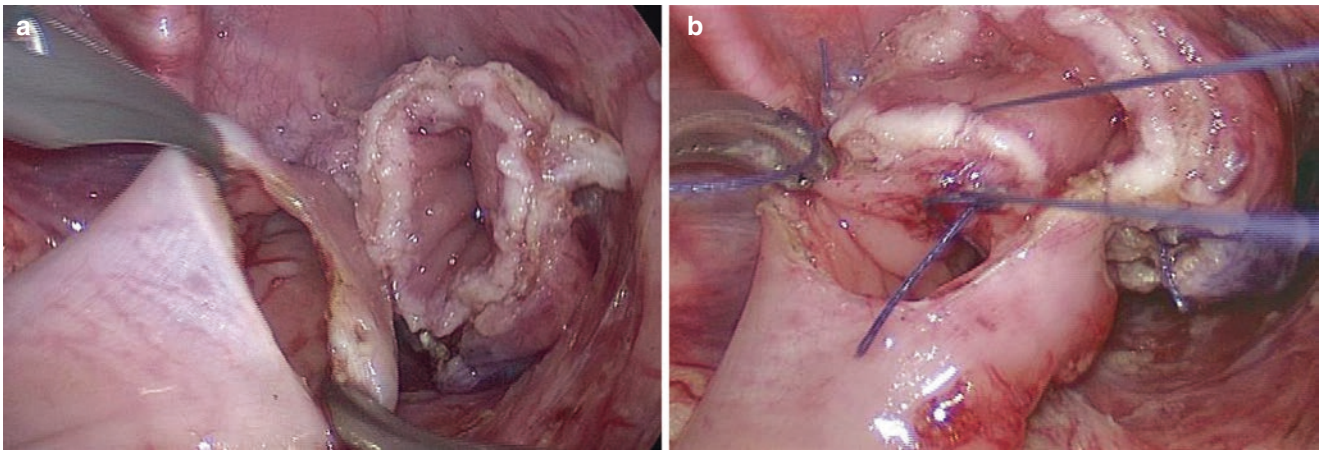

Fig. 18.7 (**a**) A transverse incision is made on the anterior wall of the colon at the level of the proximal rectal end. (**b**) The posterior wall of the upper rectum and the lower edge of the incised anterior wall of the colon are anastomosed by interrupted sutures

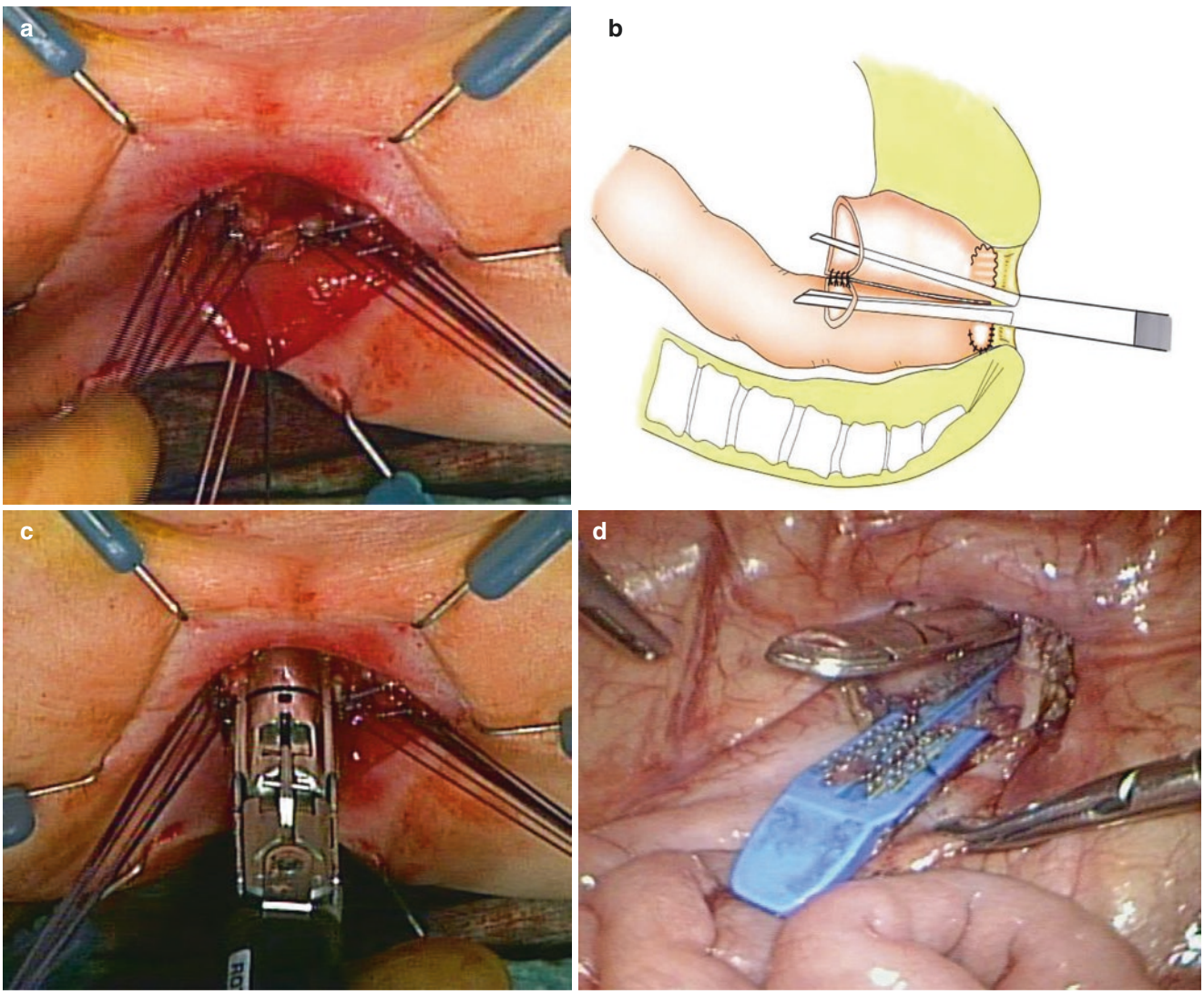

Fig. 18.8 (**a**) Anastomosis of the incised posterior wall of the rectum and the pulled-down colon. (**b**) Schema of the Z-shaped colorectal side-to-side anastomosis. (**c**) The Endo GIA is inserted through the anus. (**d**) Under laparoscopic view, the septum is completely divided

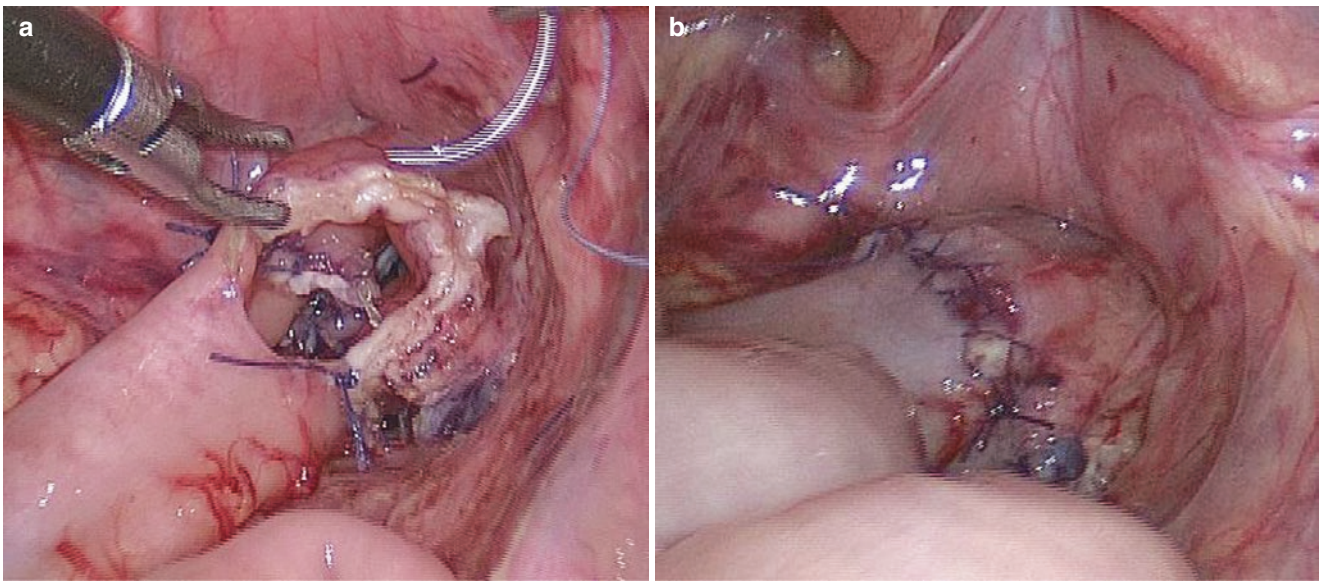

Fig. 18.9 Finally, the anterior wall of the upper rectum and the upper edge of the incised anterior wall of the colon are anastomosed laparoscopically in two layers

cartridges are applied to completely resect the septum (Fig. 18.8d). Finally, the anterior wall of the upper rectum and upper edge of the incised anterior wall of the normal colon are anastomosed laparoscopically in two layers by interrupted or continuous sutures of 4-0 vicryl, and the Z-shaped colorectal side-to-side anastomosis is completed without a blind pouch (Fig. 18.9). After the peritoneal cavity is washed using saline, a drain is placed in the pelvis via the right lower trocar site, and a transanastomotic tube is inserted via the anus for 3 days after operation for colonic decompression.

18.3 Postoperative Care

Antibiotics are continued for 3 days. A transanastomotic tube is usually removed 3 days after operation. Oral feeding is initiated on postoperative day 5. Patients undergo a digital rectal examination at 2 weeks postoperatively, and regular dilatations are performed in the outpatient clinic for 1–2 months after surgery.

18.4 Results

Between 2001 and 2016, a total of 51 children with HD underwent a laparoscopic modified Duhamel procedure. Eight children had trisomy 21. The operation was completed laparoscopically for 50 of the 51 patients. Only one patient in the early period required conversion to an open procedure because of injury to the ureter. Mean operating time was 240 min. One patient experienced a minor leak postoperatively. Two patients required late reoperation. One patient required myectomy due to sphincter achalasia, and the other patient with trisomy 21 required redo pull-through operation by the Soave procedure due to transitional zone HD. No other patients required secondary surgery. The frequency of defecation decreased gradually after surgery, and more than half of the patients experienced episodes of constipation during the early follow-up period. These patients received laxatives or enemas and showed a good response to pharmacotherapy. As the children grew older, the need for medication decreased. All patients over 4 years old, excluding the patients with trisomy 21, achieved normal defecation. No patients, except for those with trisomy 21, experienced fecal and/or urinary incontinence. Constipation can be controlled using laxatives, whereas incontinence and soiling are difficult to control. In this series, no patients over 4 years of age showed fecal incontinence.

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Ikeda Z-Shaped Anastomosis

19

Ryuichiro Hirose

19.1 Necessity of Duhamel Procedure Modification

Duhamel's retrorectal pull-through procedure was described in 1956 and avoided the extensive pelvic dissection anterior and bilateral sides of the rectum, where the pelvic plexus and nerves are densely distributed [1, 2]. The Duhamel procedure had been the most popularly performed procedure all over the world because of its several advantages: easiness of assembling procedures, less pelvic dissection, minimizing the injury of nerves around the rectum, minimal anal stretching, better visibility in entire procedure, the large anastomosis decreasing the risk for stricture, and the presence of a reservoir which is helpful for children with longer aganglionic segments. However, this procedure has a few disadvantages; the major one is the formation of the rectal blind pouch. Fecal stasis and impaction in the rectal pouch induce fecaloma formation and functional disturbances, soiling, and pressure of surrounding organs. In the severe cases, revision surgery had been necessitated [3].

Numerous modifications with using a variety of clamps and subsequently stapling devices have been employed to divide the colorectal spur, and not to make the rectal blind pouch [4–6]. Z-shaped anastomosis was devised in 1963 by Ikeda [7] to eliminate the rectal pouch and to achieve complete resection of the septum between the aganglionic rectum and the normal colon. The procedure was published in 1967. At first a specially designed oval crushing clamp was applied to perform complete resection of the colorectal septum. Subsequently stapling devices such as GIA stapler has been applied for septal incision and longitudinal anastomosis [8–10].

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19.2 Operative Procedures

19.2.1 Intra-abdominal Procedures

The patient is placed in a lithotomy position. Under laparotomy (or laparoscopy), the aganglionic segment is resected after leveling biopsies. The proximal ganglionated intestine is mobilized to ensure adequate length for the pull-through, with preserving the remaining arcades and the marginal artery. The rectum is divided near the peritoneal reflection using a linear stapling device. A retrorectal space is created with blunt dissection in the midline preferably using operator's finger or sponge peanut dissector, so that an assistant's finger can be felt at the dentate line. Recently laparoscopic approaches for intrabdominal procedures have gained popularity and become one of the standard method (Fig. 19.1).

19.2.2 Perineal Procedures

With the use of electrocautery, a full-thickness curvilinear incision is made 0.5–1 cm proximal to the dentate line posteriorly. A proximal ganglionated bowel is pulled down through the retrorectal space to the intraanal orifice. The surgeon should make certain that pulled-down bowel is not twisted, and the mesentery of this bowel is located posteriorly, so it will not be injured during the clamp crushing or firing of the stapler done later (Fig. 19.2).

19.2.3 Z-Shaped Anastomosis

Once the bowel is pulled through, the excessive portion of the pulled-down bowel is excised, and the posterior half suturing between the rectum and pulled-down ganglionated bowel is completed above the dentate line from the anal side. The anterior wall of the pulled-down bowel is anastomosed to the upper edge of the posterior intraanal orifice with the interrupted sutures to make the caudal anastomosis of septum, and some of these sutures are used for traction (Fig. 19.3).

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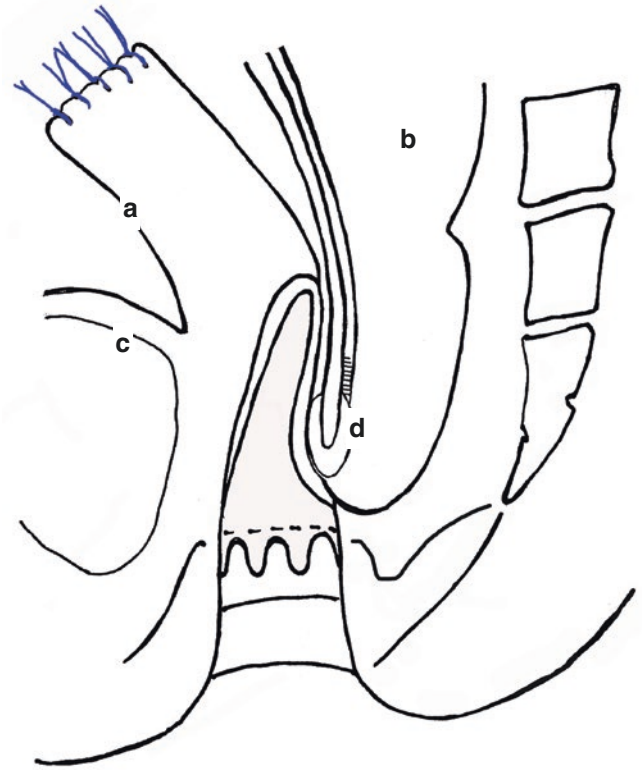

Fig. 19.1 A retrorectal space is created with blunt dissection in the midline using sponge peanut dissector. (a) Retrorectal orifice of the peritoneum. (b) Peritoneal reflection (c) Urinary bladder. (d) Sponge peanut dissector

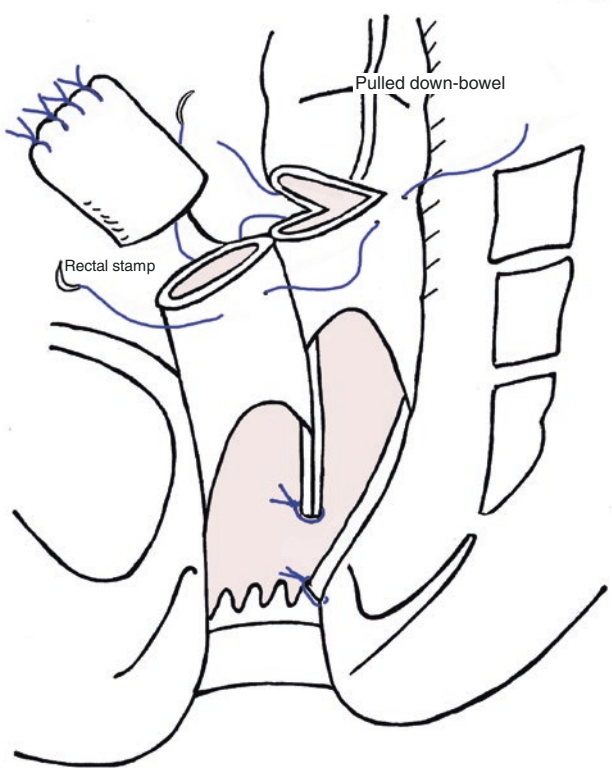

Fig. 19.2 Procedure at the peritoneal floor. Anchoring sutures placed between the rectal stamp and the pulled-down bowel. A transverse incision is made in the anterior wall of the pulled-down bowel, and the rectal pouch is transected at this level

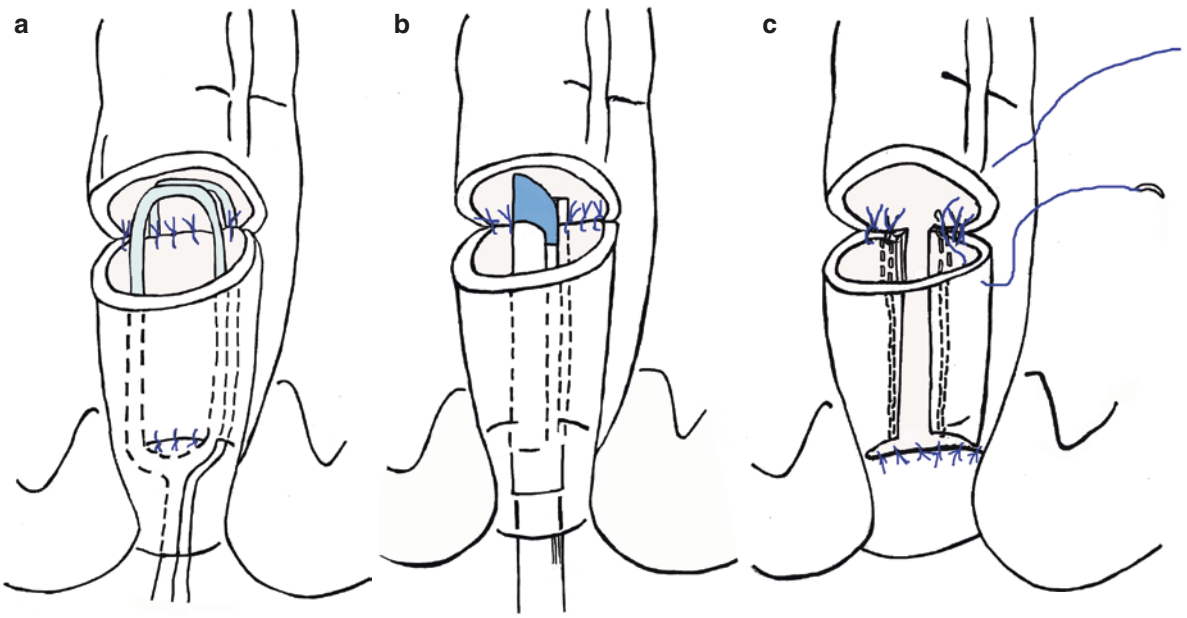

Fig.19.3 (**a**) Z-shaped anastomosis with an oval crushing clamp. Crushing anastomosis of the posterior wall of the rectum and anterior wall of the pulled down bowel by an oval crushing clamp. Interrupted sutures of the upper end of posterior wall of the rectum and anterior wall of the pulled-down bowel. (**b**) Z-shaped anastomosis using stapling device. Insertion of the stapling device into the native aganglionic rectum and the pulled-through ganglionated bowel. Sound suturing of the upper and lower end of the septum are necessary not to make gap between the upper and lower semicircular anastomosis and longitudinal stapled line. (**c**) After firing of the stapling device. After firing of the stapling device, a semicircular anastomosis is performed between the upper end of the anterior wall of rectum and of the incised anterior wall of the pulled-down bowel

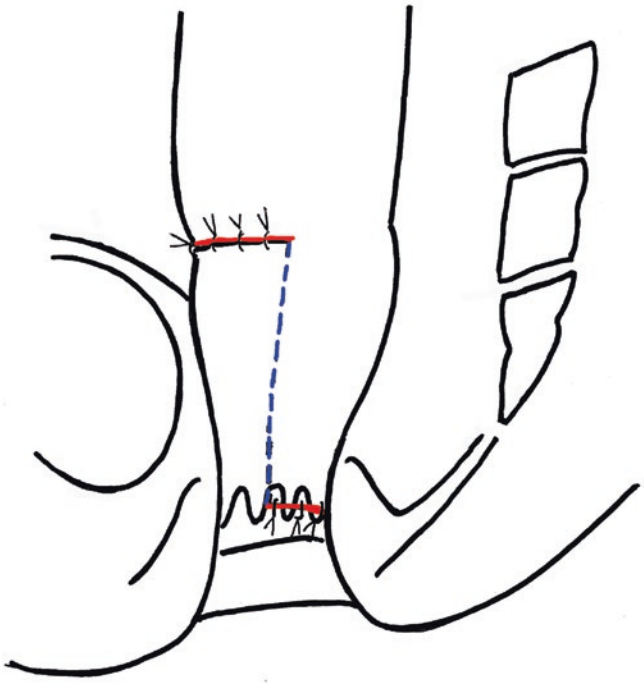

Fig. 19.4 Side view of Z-shaped anastomosis. The lateral view of this anastomosis shows a "Z"-shaped suture line, so this procedure has been named Z-shaped anastomosis

Thereafter, at the peritoneal floor, anchoring sutures are placed between bilateral side wall of the rectal stump and the pulled-down bowel from the abdominal approach. At this level a transverse incision is then made in the anterior wall of the pulled-down bowel, and the upper end of the rectal pouch is trimmed horizontally. Interrupted sutures are placed between the posterior wall of rectal stump and the lower cutting edge of the pulled-down bowel to make the cranial anastomosis of the septum. A stapling device is placed with one arm into the native anal canal and the other into the pulled-down bowel. The stapler is fired directly in the midline. In general, two or three times of staples are needed. The stapler is removed, and the integrity of the anastomosis is confirmed by inspection and palpation. The anastomosis suturing between the anterior wall of the rectal stump and upper cutting edge of the pulled-down bowel is completed. This simple additional procedure will enable to relieve the blind pouch completely (Fig. 19.4).

A drainage tube was inserted in Douglas' pouch, and the abdomen is closed in the usual fashion.

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Soave's Procedure

20

Motoi Mukai, Koji Yamada, Masakazu Murakami, and Ryuta Masuya

20.1 Introduction

Soave described his new technique as endorectal pull-through for Hirschsprung's disease (HD) in 1963 [1, 2]. Endorectcal pull-through is one of three major procedures of definitive operation for HD. The remaining two are Duhamel procedure and Swenson procedure. Endorectcal pull-through consisted in removing the mucosa and submucosa of the rectum and pulling ganglionic intestine through the aganglionic muscular cuff. He introduced a basic concept of this operation from that of imperforated anus. In 1955 Romualdi reported on the treatment of high imperforate anus by the removal of the mucous membrane of the rectum down to the fistula and pull-through of the malformed rectal canal deprived of its epithelium [3]. Soave thought that Romualdi's technique could be applied in the treatment of HD.

He first performed this operation on a 2-year-old boy in 1961 [3]. His first reports [1, 2] were published after treating six children with endorectal pull-through. He published English articles about the surgical technique of endorectal pull-through one after another in *Surgery* in 1964 [4], in *Arch Dis Child* in 1964 [5], in *Br J Surg* in 1966 [6], and in *Curr Probl Surg* in 1978 [7]. He spoke at 15th Annual Meeting of the American Pediatric Surgical Association on the subject of 20 years' experience of endorectal pull-through [3].

Boley published an article titled "New modification of the surgical treatment of Hirschsprung's disease" in 1964 [8]. His article appeared in *Surgery* along with the Soave's article [4]. Boley's procedure consisted of three major steps. Step 1 would be the resection of the aganglionic colon above the peritoneal reflection and mobilization of the normal colon to permit anastomosis to the anus. Step 2 would be the removal of the mucosa of the distal rectum by transabdominal and transanal approach. Step 3 would be the anocolonic anastomosis. Although Boley's procedure has a lot of similarities to Soave procedure, it differs in the following points: he performed rectal mucosal dissection after transecting aganglionic colon above the peritoneal reflection, and he made a primary anastomosis between ganglionic colon and anus.

Soave believed the anastomosis should be postponed for 8–10 days after the pull-through in view of safety and future function. He allowed a segment of the pulled-through colon to protrude well beyond the anal skin margin for removal at a second stage 8–10 days later.

In Australia over a 4-year period from 1997 to 2000, the Soave procedure had been the commonest operation, followed by Duhamel's pull-through [9].

Japan has a retrospective nationwide survey for four decades, which assessed the changing profile over time [10–12]. Original and modified Soave procedures, except for transanal endorectal pull-through (TAEPT), account for 26.3% of the optimal operative procedures from 1978 to 1982, 20.7% from 1988 to 1992, 18.8% from 1998 to 2002, and 23.5% from 2008 to 2012, respectively [12].

Although few pediatric surgeons are thought to perform original Soave procedure because of establishment of laparoscopic procedures and TAEPT, we will describe the Soave procedure based on articles written by Soave [3–7].

20.2 Operative Technique

20.2.1 Preoperative Treatment

Soave performed preliminary colostomy only in newborns with severe ileus and when enterocolitis occurred. Preoperatively dilatation of the anus and the internal sphincter under anesthesia was performed 2–3 times prior to the operations, particularly to patients with colostomy. Dilation was repeated in the operating room at operation day to permit easier pull-through of the hypertrophied colonic segment.

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20.2.2 Patient Position

The patient is positioned supine with buttock placing at the edge of the operating table (Fig. 20.1). The lower limbs hang freely, and they are draped and held in a pocket to prevent slipping of the patient's pelvis. The operating table is flexed in slight Trendelenburg positon. The abdominal extra mucosal dissection should be carried out under constant visual control as far as possible. This combined positioning gives optimum pelvic exposure and easy access to the rectal canal abdominally. First Soave completed mucosal dissection from below transanally through a circumferential mucosal incision following transabdominal dissection [4]. However, this patient position could eliminate the need for transanal mucosal dissection and complete mucosal dissection transabdominally.

20.2.3 Dissection of the Seromuscular from the Mucosal and Submucosal Layer of the Rectum

A long, left paramedian rectus-retracting incision is originally made (Fig. 20.1). The narrow aganglionic segment is exposed above the peritoneal reflection, and procaine hydrochloride, 0.5% solution, is infiltrated into the anterior antimesenteric seromuscular coat of the rectosigmoid segment 8–10 cm above the peritoneal pelvic reflection to facilitate the separation of the seromuscular from the mucosal layer (Fig. 20.2). Separation of the seromuscular from the mucosal layer is the most technically difficult and peculiar step of Soave procedure.

A longitudinal seromuscular incision is made on the previously infiltrated anterior wall of the rectum. Separation of the seromuscular layer from the mucosal layer is begun with two gauze balls. The edges of the seromuscular layers are held by atraumatic forceps to allow tractions. Soave highlighted the importance of preservation of the superior hemorrhoidal artery as it carries the main blood and nerve supply to the rectal muscular cylinder. The seromuscular cylinder is progressively dissected from the submucosa and mucosa, passing first laterally, alternately, on the left and right side and posteriorly. The dissection of the posterior aspect of the seromuscular coat has been completed, and the mucosal tube is freed completely, laterally and posteriorly (Fig. 20.3). The muscular rectal cuff is divided circumferentially, and the sleeve is clamped with atraumatic forceps for traction. The dissection is progressively carried downward under constant visual control as far as possible. As the detachment proceeds,

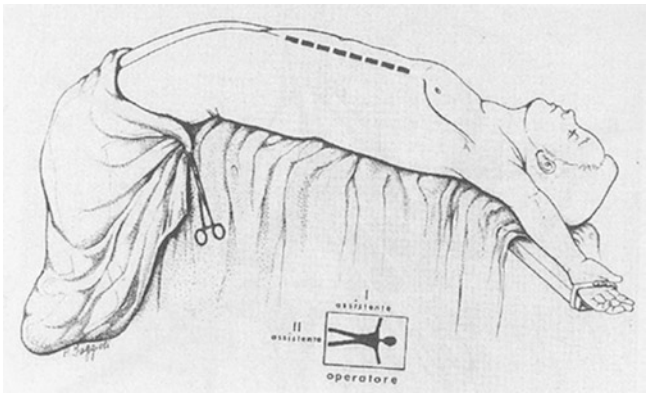

Fig. 20.1 Patient position and left rectus skin incision

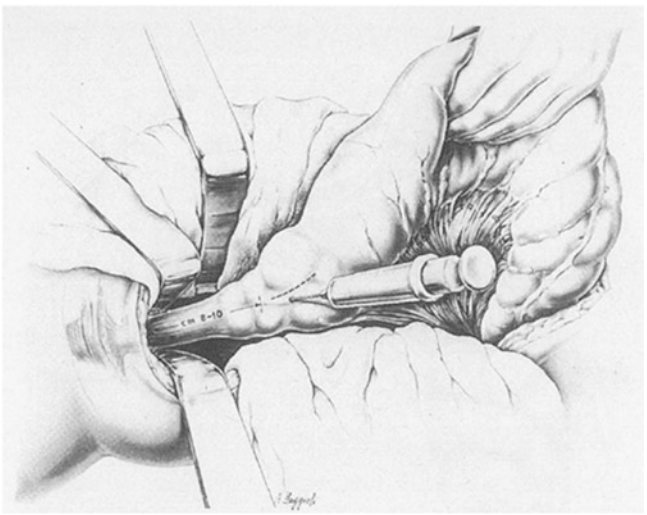

Fig. 20.2 Procaine hydrochloride injection submucosally to facilitate the separation of the seromuscular from the mucosal layer

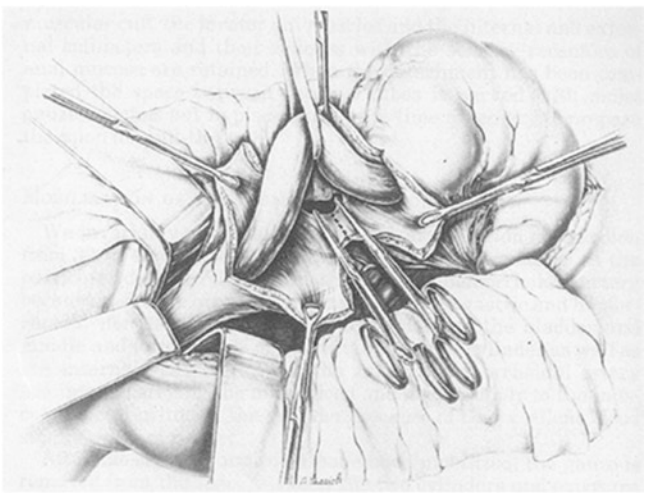

Fig. 20.3 Separation of the muscularis from the submucosa circumferentially

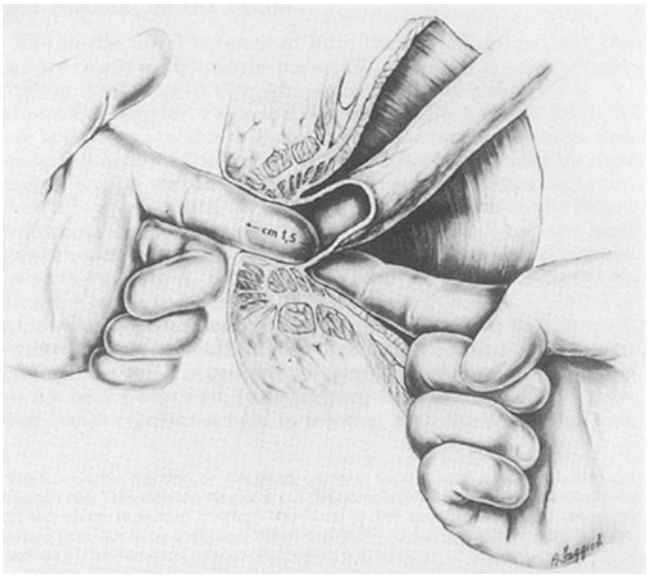

Fig. 20.4 Separation of the seromuscular from the mucosal layer is completed when a distal level of 1–1.5 cm from the pectinate line is reached

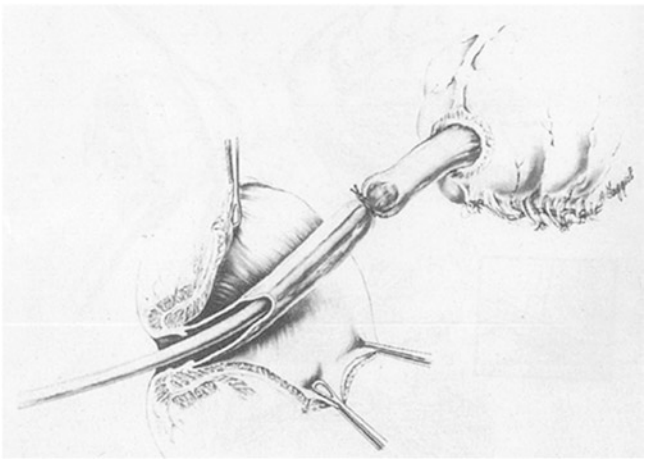

Fig. 20.5 A metal Pezzer is introduced through the anus to evert the mucous tube and pull through the ganglionic colon

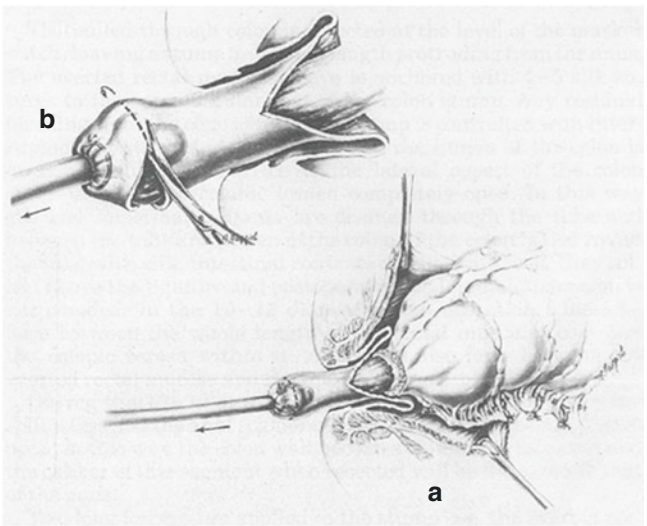

Fig. 20.6 Everted mucous tube is cut and pull through the ganglionic colon

unlike the seromuscular coat, the mucous coat stretches. The dissection is easier along the posterior wall of the rectum than along the anterior wall. The use of delicate malleable retractors and of the operator's finger may be very useful in dividing residual adhesions and in separating the distal rectal muscular cuff from the internal mucosal tube. If the recto-anal canal is hypertrophied and inflamed, the dissection is more difficult. The depth of the dissection may be checked by inserting an index finger in the anus and inserting a finger between the overturned muscular cylinder and mucosal tube in the abdominal cavity. Detachment is completed when a distal level of 1–1.5 cm from the pectinate line is reached (Fig. 20.4). A very low endorectal dissection is very important because pulled-through colon make a retrograde move into the anal canal after cutting for secondary anastomosis.

20.2.4 Pull-Through Procedure

The anal region is exposed by raising the lower limbs to 70°. One of the operating surgeons then moves to the foot of the table. A metal Pezzer catheter is introduced through the anus into the rectal mucous cylinder, and a strong silk ligature is tied around the mucous cylinder just below the head of the Pezzer catheter (Fig. 20.5). Gentle traction of the Pezzer catheter pulls the mucous cylinder down and everted. The everted mucous sleeve is cut circumferentially, and further traction on the head of Pezzer drew the proximal normoganglionic colon through the muscular sleeve consecutively (Fig. 20.6). After the pull-through procedure is completed outside the anus, there are two concentric cylinders: external everted rectal mucosa and internal ganglionic colon. The proximal edge of the intra-abdominal rectal seromuscular cylinder is sutured to the seromuscular layer of the pull-through ganglionic colon. No sutures are placed posteriorly, so as to leave the blood supply intact. A Penrose drain is placed into the abdominal cavity from between the colon and the rectal muscular cuff and brought out through posterior to the external sphincter muscle of the anus and out pararectally. The pulled-through colon is transected, leaving a stump 5–7 cm in length protruding from the anus. The everted rectal mucous sleeve is anchored with suture to the seromuscular coat of the colon stump. Intraluminal tube in the pulled-through colon is placed to leave the colonic lumen completely open (Fig. 20.7).

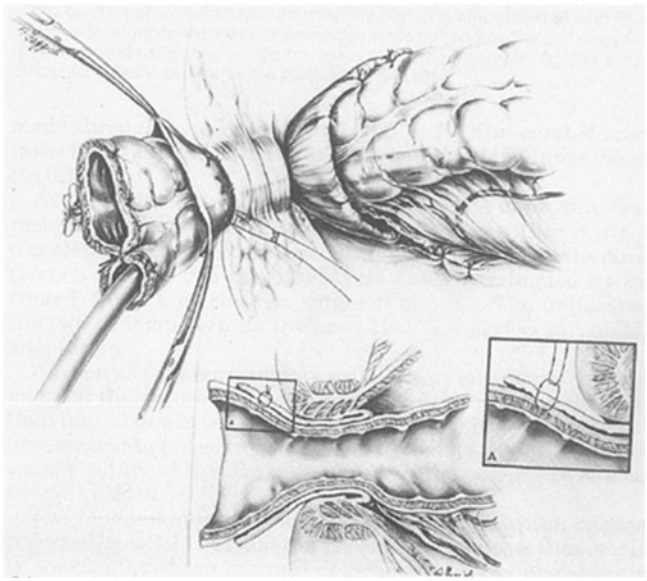

Fig. 20.7 The pulled-through ganglionic colon is resected leaving a 5- to 7-cm-long stump protruding from the anus. The everted rectal mucosal sleeve is anchored to the seromuscular coat of the colon stump. An intraluminal tube is anchored to the lateral aspect of the colon not to close the colonic lumen

20.2.5 Resection of the Protruding Rectal Stump (Secondary Anastomosis)

In 8–10 days after the pull-through operation, adhesions form between the whole length of the rectal muscular coat and the colonic serosa, which adheres to the everted rectal mucosa too. Over this time period, the exteriorization of the colon keeps the sphincter and the anal segment which compresses the colon wide open; in this way the colon wall of this segment will become proper size for the anus.

Eight to ten days later, the protruding colon stump and rectal mucosa are transected close to the anus by electrocautery. Two mucosal layers are approximated with interrupted sutures (Fig. 20.8). After approximation the stump spontaneously retract into the anal canal.

20.3 Morbidity and Mortality

From 1961 to 1983 Soave performed endorectal pull-through in 271 HD patients [3]. From 1961 to 1966, 34 patients underwent original endorectal pull-through without eversion of

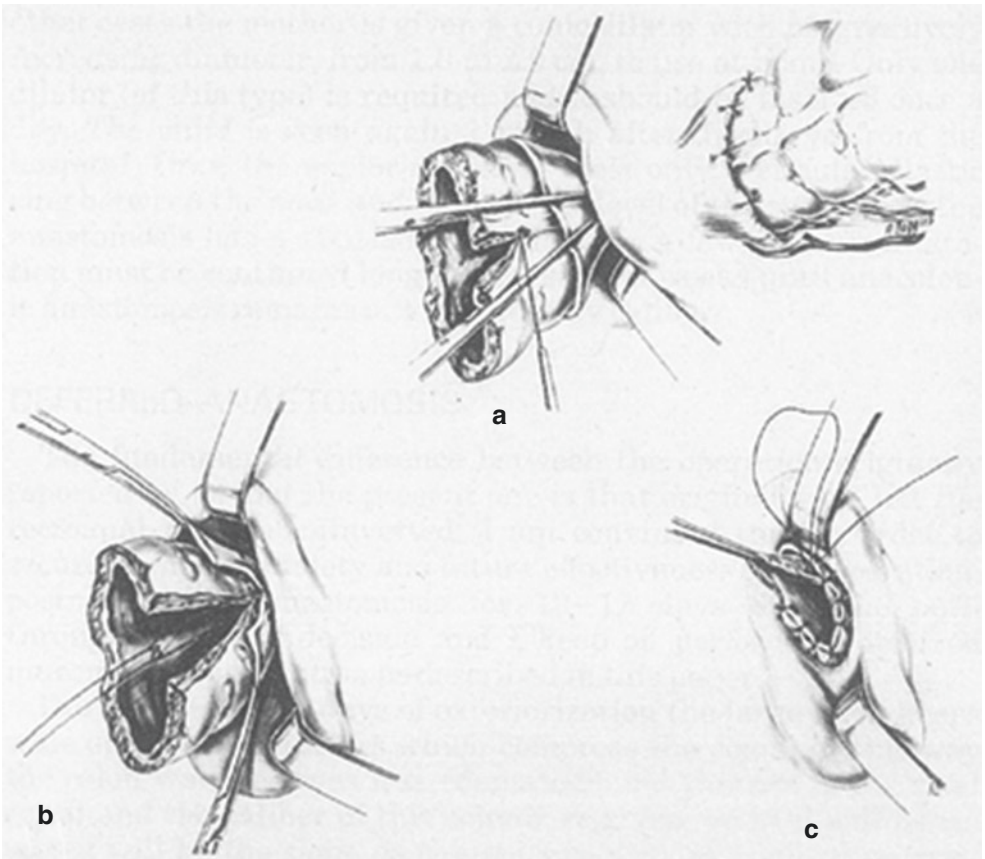

Fig. 20.8 The residual stump is amputated, and a mucosa-to-mucosa anastomosis is made

rectoanal mucosa. From 1966 to 1983, 237 patients underwent mucosal dissection only transabdominally and modified endorectal pull-through with eversion of rectoanal mucosa.

Soave had 12 dead cases intraoperatively and postoperatively; three cases with intraoperative cardiac arrest, two cases with intraoperative anesthetic complications, three cases with massive bilateral pulmonary atelectasis, and four cases with peritonitis due to perforation of the pulled-through colon.

There were nine (3.4%) postoperative complications with recovery. Four patients had abscesses within the muscular cuff which occurred with the original technique (1961–1966). Retraction of the pulled-through colon stump occurred in three patients who underwent the original technique (1961–1966). They had second operation which required extensive mobilization of the left and transverse colon. Necrosis of the pulled-through colon stump within the seromuscular tube occurred in two patients due to operative technical error. There was no cases with anastomotic leak because the Soave procedure is without primary anocolon anastomosis.

There were 13 (4%) postoperative complication unrelated to the endorectal pull-through: three patients with small bowel obstruction, five patients with pelvic abscess, and five patients with delayed wound healing.

Recurrent constipation occurred in five patients because the aganglionic segment had not been completely removed proximally and when the internal sphincter had not been adequately weakened during the pull-through. Enterocolitis occurred in the immediate postoperative period in 5–6% of the cases.

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Soave-Denda-Boley Procedure

21

Tatsuo Kuroda

Following after the report of the first successful definitive surgery for Hirschsprung's disease described by Swenson and Bill in 1948 [1], modification and novel development of the surgical procedures were described one after another in the 1950s and 1960s. The three satisfactory procedures were finally established: Swenson's abdominal prolapse technique, Duhamel's retrorectal transanal pull-through, and Soave's submucosal endorectal pull-through technique. The latter two procedures were furthermore modified later. In the present chapter, Soave-Denda-Boley procedure, a modified technique of Soave's procedure with a primary suture of the colon to the anal site and its clinical results are presented.

21.1 Historical Background

Although the abdomino-anal pull-through procedure originally described by Swenson and Bill [1] in 1948 provided satisfying clinical results, a couple of potential problems such as the bowel symptoms related to the residual rectum and the surgical injury to the pelvic nerve fibers were pointed out on the other hand. Rehbein and von Zimmermann [2] reported in 1960 that some of their patients required repeated bougienage and follow-up barium enemas showed the dilatation of colon. The original Swenson's procedure was modified in order to solve these problems, whereas two novel techniques for Hirschsprung's disease were additionally described: one by Duhamel [3] in 1956 and another by Soave [4] in 1964.

Soave developed the endorectal pull-through procedure with a mucosal resection of the aganglionic rectum similar to the previously reported technique used for familial polyposis proposed by Ravitch [5] and other techniques for rectal agenesis described by Rehbein [6] and by Romuraldi [7]. In this procedure, the normoganglionic colon was brought down to the anal site through the rectal muscular cuff created by the stripping of the mucosal layer. In the original Soave's procedure, the pulled-through colon was remained unsutured until the completion of auto-anastomosis. Denda and Katsumata modified Soave's procedure to suture the normoganglionic colon primarily to the anal canal, which was first published in a non-English journal in 1966 [8]. Boley et al. [9] also reported the similar technique in 1968. Thus, this technique is now called Soave-Denda-Boley procedure and became one of the most common definitive operations for Hirschsprung's disease.

21.2 Operative Technique

In a long time since the first description of Soave-Denda-Boley procedure, the technique has been altered little by little. The practical procedure performed in the 1980s by the successor of Denda is explained below.

In Soave-Denda-Boley procedure, the patient is placed in the semi-lithotomy position or the position in which both of transabdominal and transanal approach can be performed. The laparotomy and the initial exploration of the intestines are identical with the original Soave's technique. After laparotomy, length of the narrow segment is examined, and the biopsy is taken from the intestine slightly above the dilated segment in order to confirm the presence of the normal ganglion cells. In the cases with stoma, the stoma site is generally brought down to the anal site. The distal colon is mobilized and then dissected at the slightly proximal level (about 2–5 cm) above the lower limit of normoganglionic segment using a stapler.

The distal colon and rectum are further more mobilized with dissection of the peritoneum around the peritoneal reflection. Mesorectum is divided after ligation of the rectal vessels to avoid hemorrhage during the mucosectomy.

Then, saline is injected in the submucosal space of the rectum above the peritoneal reflection in order to assist blunt dissection of the mucosa from the intrinsic muscle layers (Fig. 21.1).

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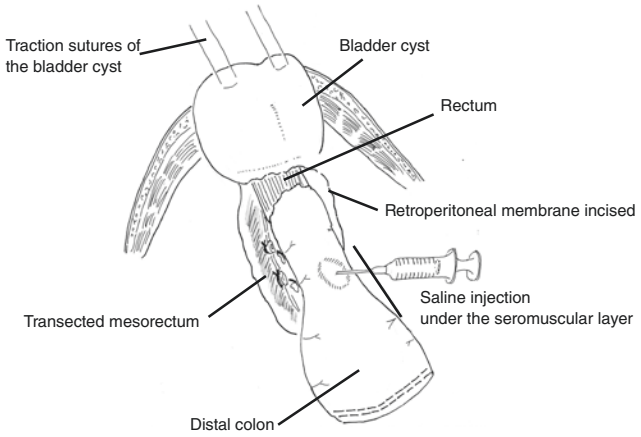

Fig. 21.1 Saline injection under the seromuscular layer for stripping

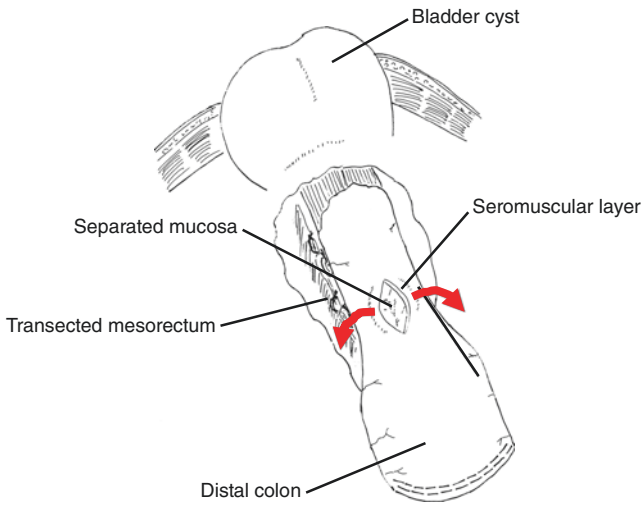

Fig. 21.2 Vertical seromuscular incision to strat stripping

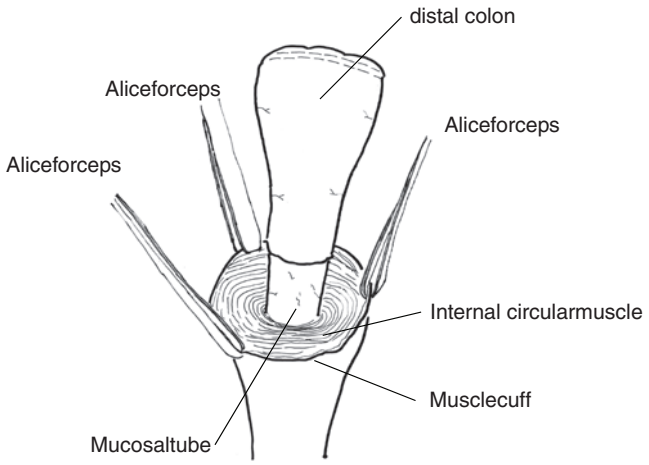

Fig. 21.3 Mucosectomy (stripping) procedure

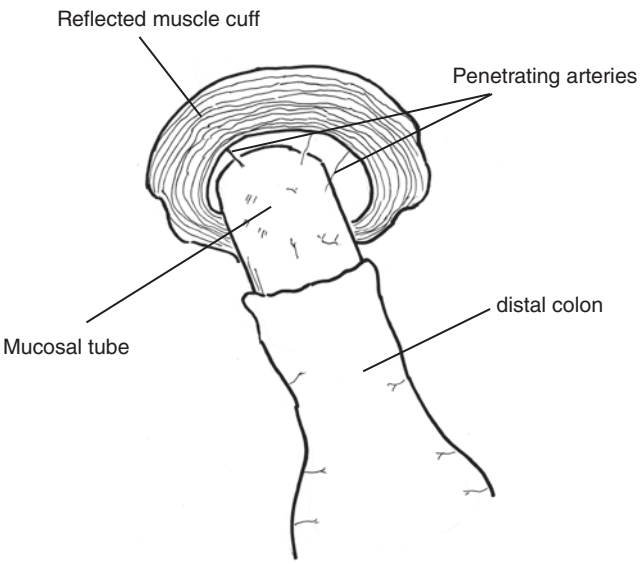

Fig. 21.4 Reflection of the muscle cuff for further stripping

The rectal serosa is incised along the long axis to strat the stripping procedure, and then the seromuscular layer and the mucosal layer are dissected (Fig. 21.2). Penetrating vessels in the rectal wall are coagulated using electric cautery. At first, the mucosal layer and the muscle layer are separated whole around the initial level where saline is injected, and then the seromuscular layer is transected to remain the mucosal tube. Separation of the mucosal layer is directed toward the anal sites. The proximal muscle cuff is grasped by Allis forceps and pulled upward (Fig. 21.3), and thereafter, the cuff is reflected according to the progress of separation (Fig. 21.4). During this procedure, circular layer of the intramural muscle is recognized inside the muscle cuff, which indicates that the separation is in progress at the suitable layer.

Separation of the mucosal layer is continued down to the pelvis until the dentate line is identified. Finally, mucosal tube is transected 5 mm above the dentate line; thus the lower aganglionic segment is resected together with the transition segment.

The proximal colon with normal ganglia confirmed by the intraoperative rapid pathological examination is then brought down to the anus through the muscle cuff. The seromuscular layer of the colon is sometimes sutured with the inside of the muscle cuff at the level of 2–3 cm above the dentate line in four directions.

The upper half of the pulled-through colon was opened above the stapled line, and the whole layer of the colon was sutured with the mucosa and the submucosal layers of the rectum immediately above the dentate line by interrupted sutures (Fig. 21.5). Thereafter, lower half of the pulled-through colon was resected and similarly sutured to the rectal mucosa.

In the initial experience of Denda's modification of Soave's procedure, some complications were observed during the short postoperative period, and a couple of novel

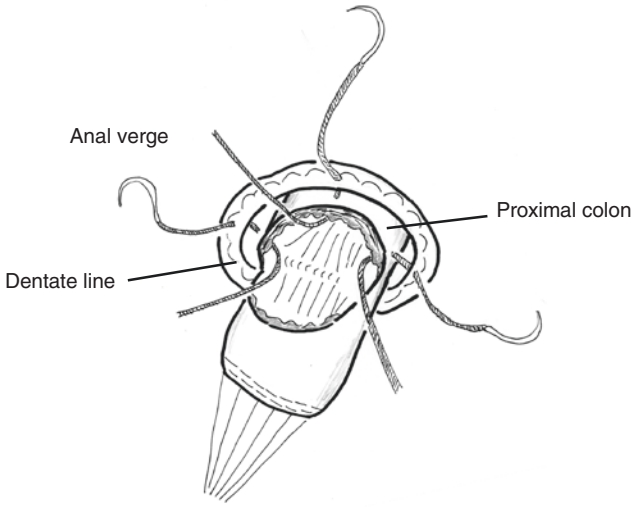

Fig. 21.5 Transanal suture

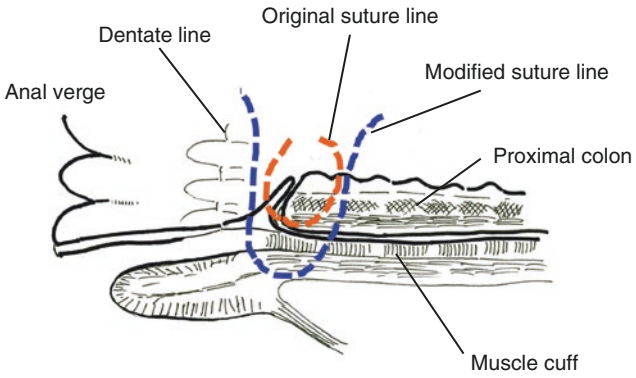

Fig. 21.6 Remediation of the transanal suture technique

improvements were furthermore added to the Soave-Denda-Boley procedure by Denda and his colleagues.

First problem was the relatively high incidence of anastomotic insufficiency and leakage that resulted in peritonitis and required creation of stoma. Later, ischemia of the rectal mucosa at the anal site was proved to be the cause of the anastomotic insufficiency. The procedure was altered then, and not only the mucosa but also the submucosal layer and the deeper tissue were sutured together with the whole layers of the pulled-through colon in the transanal anastomosis as shown by the blue broken line in Fig. 21.6. Thereafter, the incidence of anastomotic insufficiency decreased drastically.

Second problem was persistent sphincter achalasia after the operation, which sometimes requires enema and additional bowel management. As for Soave's technique, necessity of postoperative dilation was also pointed out in order to avoid organic and functional stenosis of the anus. Successors of Denda added a myectomy or myotomy of the internal anal sphincter, that is, transanal dissection of the

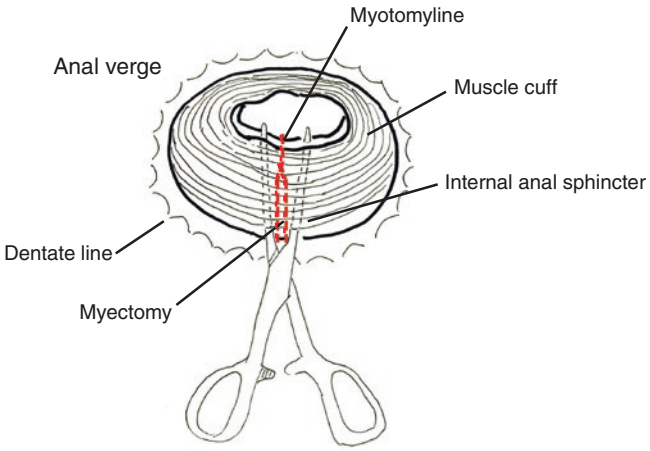

Fig. 21.7 Myectomy and myotomy of the internal anal sphincter at 6 o'clock of the anus

muscle cuff at the position of 6 o'clock of the anus before anastomosis according to Lynn's technique (Fig. 21.7). This procedure decreased the incidence of the postoperative symptoms due to sphincter achalasia and is widely accepted in Japan, whereas the myectomy or myotomy procedure is not necessarily added outside of Japan. The postoperative sphincter achalasia may be self-limiting in most of the cases, and there may be the slight risk that the excessive myectomy causes incontinence during the long postoperative period.

21.3 Clinical Results

The clinical results of Soave-Denda-Boley procedure were precisely examined and reported by Denda's colleagues and successors in Japan. According to their initial report in 1983 [10], the number of bowel movement immediately after the operation was relatively high, which gradually decreased by age: 1–5 (averaged 2.8) times a day until the age of 3 years, averaged 2.1 times a day between the age of 3 and 7 years, and 1–2 (averaged 1.7) times a day after the age of 7 years. A support for defecation was required in 38% at the age before 3 years and 18% at the age between 3 and 7 years, respectively. Only a few patients need enema once in a couple of days. A desire to stool was recognized from early postoperative period. Sixty-five percent of the patients had the complete sense of desire to stool at the age between 3 and 7 years, which furthermore raised up to 91% after the age of 7 years.

At the age between 3 and 7 years, 61% of the patients showed no soiling, and 12% had soiling only at the time of diarrhea. After the age of 7 years, 70% of the patients had soiling, and 24% had soiling only in case of diarrhea. However, slight staining of the undershirts was observed in 56% of the patients at the age between 3 and 7 years. After the age of

7 years, only 21% had staining more than twice a week, and other 21% developed staining only in case of diarrhea.

In the manometrical assessment, 37% of the patients showed positive anorectal reflex before the age of 7 years. Furthermore in the group aged over 7 years, 44% showed the positive anorectal reflex. Later report by Morikawa et al. [11] in 1989, positivity of anorectal reflex was observed in 39% of the patients. However, Morikawa also reported that normal rhythmic activity of the anorectum was seen in 72%, and 90% of the patients showed good continence 10 or longer years after the operation.

It has been considered at present that there is no significant difference in the postoperative anorectal function between the patients who underwent Soave-Denda-Boley procedure and those who underwent Duhamel procedure in the long postoperative period.

21.4 Later Advancement of the Procedure

One of the important significance of Soave-Denda-Boley procedure consists in that the procedure popularlized the endorectal pull-through technique. Actually, Soave-Denda-Boley procedure and Duhamel procedure including its modification techniques were the two major definitive operations for Hirschsprung's disease until the early 1990s. Subsequently in the 1990s, laparoscopic surgery was introduced and widely spread in the pediatric surgical field. In 1995, Georgeson [12] described laparoscopic Soave's procedure, that is, endorectal pull-through technique performed in 12 cases. The report by Hoffman et al. [13] in 1996 and the report by Rothenberg et al. [14] in 1997 followed after Georgeson's first report and presented the successful completion of the laparoscopy-assisted endorectal pull-through procedure in infants and children. Thus, the laparoscopic Soave's procedures were established and widely spread as the definitive surgery for Hirschsprung's disease. The reports of laparoscopic Duhamel's procedure were also seen including the early description by Smith [15] in 1994. However in general, the endorectal pull-through technique is simpler compared to the retrorectal pull-through technique when assisted by laparoscope; therefore the former was preferred by more pediatric surgeons.

Another major innovation was described regarding the endorectal pull-through technique for Hirschsprung's disease also in the 1990s. Saltzman et al. [16] described the transanal mucosal resection instead of the conventional transabdominal technique in Soave's procedure in 1996. Thereafter, De la Torre-Mondragon and Ortega-Salgado [17] first described the totally transanal endorectal pull-through procedure in 1998. Since then, there has been no need for laparotomy to complete the Soave-Denda-Boley procedure in the selected cases with relatively short aganglionic segment. As shown above, Soave-Denda-Boley procedure has been innovated until now since the first description in the late 1960s according to the advancement of surgical technology because of its high potential in evolvability.

21.5 Future Aspects

At present, there remains a less situation in which the original Soave-Denda-Boley procedure with open laparotomy is performed for Hirschsprung's disease because of the wide spreading of the laparoscopic techniques. Therefore, one of the future tasks regarding Soave-Denda-Boley procedure may be the long-term management for the adult patients who were operated with the procedure while in their childhood. The suitable operation for total colonic aganglionosis has not been fully established. Whether Soave-Denda-Boley procedure can be selected as a proper definitive surgery for total colonic aganglionosis or not should be verified in the future studies.

Also precise assessment would be required regarding the long-term results after the relatively new endorectal pull-through procedures developed from the Soave-Denda-Boley procedure.

Since Soave-Denda-Boley procedure has become the most common definitive operation for Hirschsprung's disease in the present days, many future tasks still remain to be completed.

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22 Transanal Endorectal Pull-Through for Hirschsprung's Disease in the Neonate and Early Infant

Kosaku Maeda

Surgical treatment of Hirschsprung's disease has changed significantly during the last two decades. The recent introduction of minimally invasive pull-through techniques may accelerate the primary definitive operation to be performed at further earlier period.

One-stage surgery for Hirschsprung's disease is well established, and the results are comparable or better than after two- or three-stage operations. Primary endorectal pull-through in the newborn period was first described by So et al. in 1980 [1]. 18-year follow-up of these patients was reported, and 81.5% of the patients were totally continent, whereas there was no recurrence of obstructive symptoms [2]. The rationale for primary surgery in the neonatal period has been the potential benefit of avoiding a colostomy during the first months of life and establishment of colonic continuity early in life. This may enhance the development of normal continence.

In 1995, Georgeson et al. described a minimal access approach, consisting of a laparoscopic mobilization of the sigmoid colon and proximal rectum, and a submucosal sleeve was developed transanally to meet the dissection from above [3]. The colon was then pulled down in continuity, divided above the transitional zone, and secured to the anal mucosa 5–10 mm above the pectinate line. Following reports documented a short time in the hospital, and early results were equivalent to those reported for the open procedures with a superior cosmetic result.

The total transanal Soave procedure represented a natural evolution from the laparoscopic operation. Transanal resection of the rectum was shown to be possible in the initial series of children with Hirschsprung's disease published by de la Torre and Ortega-Salgado. They first described totally transanal endorectal pull-through in 1998 [4]. The reported series of patients having undergone totally transanal pull-through include some neonatal patients, but the potential problems associated with neonatal surgery for Hirschsprung's disease have not been addressed before in the context of a totally transanal procedure [5]. The transanal approach has the principal benefit of avoiding the need for intra-abdominal mobilization of the rectum through either laparotomy or laparoscopy.

Long-term functional outcome of patients having transanal pull-through is unclear, but short-term function is reported to be very similar to that after open or laparoscopic procedures. One-stage neonatal repair of Hirschsprung's disease has been suggested to be associated with less cost and demand of resources without jeopardizing functional outcome [6–8].

This chapter ascertains the feasibility and safety of totally transanal pull-through in the neonatal period with organized approach to the common problem of obstructive symptoms after the transanal pull-through.

22.1 Preoperative Considerations

In the neonate, Hirschsprung's disease must be differentiated from other causes of intestinal obstruction, including meconium ileus, intestinal atresia, anorectal malformation, and malrotation. Careful history and physical examination, abdominal X-ray, and contrast enema are the initial diagnostic maneuvers in most cases.

The definitive diagnosis of Hirschsprung's disease is made on the basis of a suction rectal biopsy, looking for the presence or absence of ganglion cells and of hypertrophic nerves. Recently almost all pathologists use cholinesterase staining to complement the standard histologic evaluation. The biopsy must not be taken too close to the dentate line, because there is normally a paucity of ganglion cells in this location.

Rectal and colonic decompression and irrigation with a transanally inserted tube are widely used in the preoperative management until primary pull-through for the cases with short-segment aganglionosis. After the child has been stabilized, the definitive surgical procedure can be done

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semielectively. During the waiting period, most children can be fed breast milk or an elemental formula, in combination with rectal stimulations or irrigations.

22.2 Surgical Technique

For the operation, the patient was placed in a prone position with the pelvic elevated. As a first step to the transanal mucosectomy of the rectum, the anal canal was exposed with the Lone Star retractor system™. The hooks of a circumferential retractor system are placed initially just the anal canal at the level of the mucocutaneous junction.

The operation starts with a circumferential mucosal incision 5 mm above the dentate line. The distance above the dentate line depends on the size of the child, but it is crucial that the incision be high enough above the dentate line (5–10 mm) so that the transitional epithelium is not damaged. This is important to prevent loss of sensation, which may predispose the child to long-term problems with incontinence (Figs. 22.1, 22.2).

5-0 monofilament sutures are placed in the mucosa, after the mucosal incision, to provide traction on the mucosal edge during the mucosal dissection. The mucosa is stripped from the underlying muscle for a variable distance, initially using a fine-tipped needle electrocautery and subsequently using blunt dissection (Fig. 22.3).

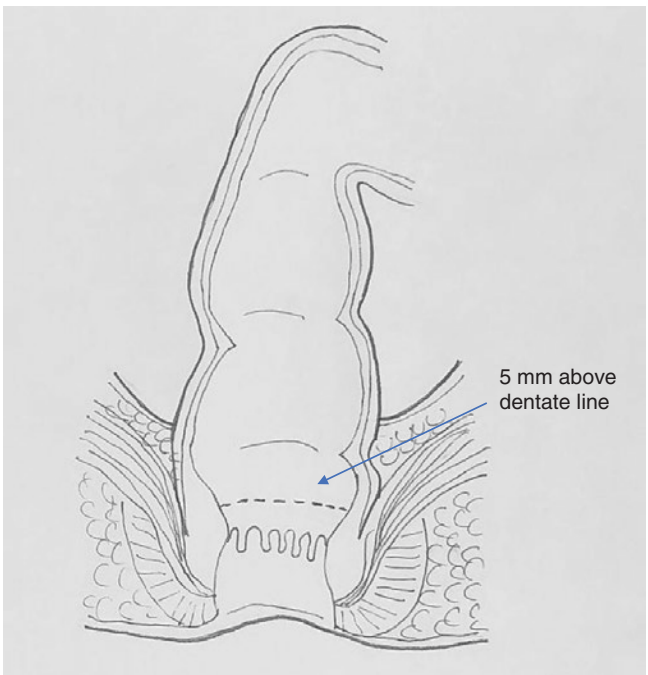

Fig. 22.1 Mucosal incision 5 mm above dentate line

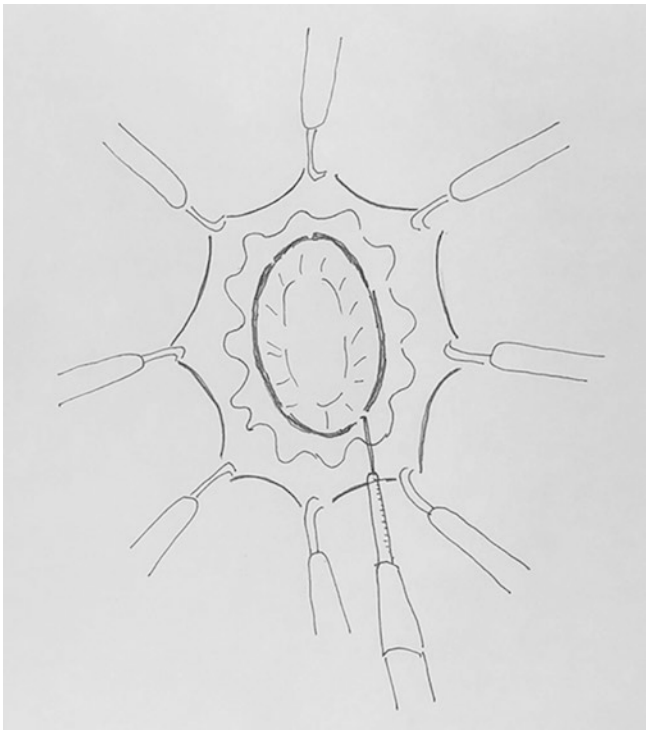

Fig. 22.2 A circular incision is made in the rectal mucosa

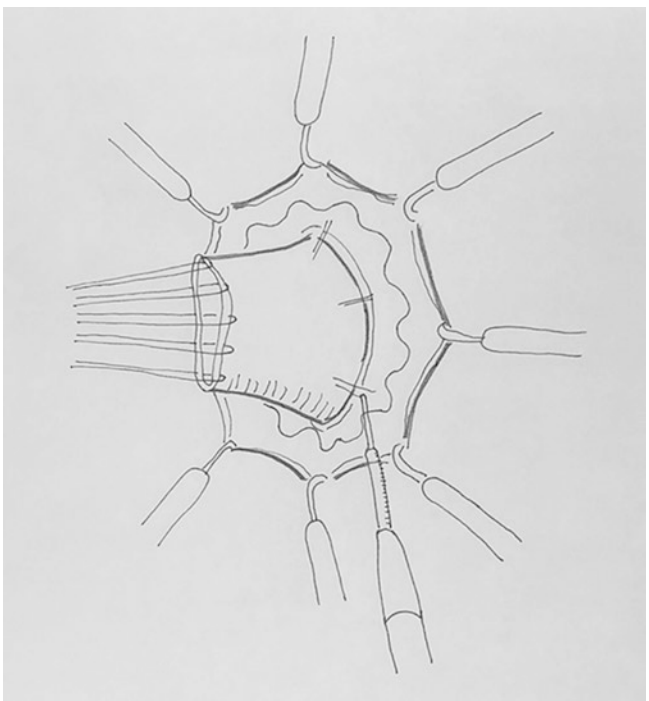

Fig. 22.3 The submucosal dissection is continued using fine-needle diathermy

The transanal submucosal dissection was extended above the extramuscular plane (Fig. 22.4). An incision was then made in the rectal muscle posteriorly to join the dissection from above. The smooth muscle fibers of the rectal sleeve were then divided circumferentially at this level. This muscle was also split posteriorly down to the proposed anastomotic line to accommodate the ganglionated colon to be pulled through the sleeve (Fig. 22.5). The rectum and sigmoid colon were then pulled down through the rectal sleeve in continuity.

It is important that the vessels be divided just as they enter the bowel wall, to avoid injury to pelvic nerves and vessels, as well as the prostate or vagina. It is also important to avoid twisting of the bowel as the dissection progresses proximally. This can be accomplished by making sure that the orientation of the intestinal wall does not change.

A full-thickness biopsy was sent to the pathologist for frozen section confirmation of the presence of ganglion cells. When the normally innervated bowel is reached, the bowel is divided a variable distance (4–6 cm) above the transitional zone. The colon was then transected above this point, and the anastomosis is performed.

A single-layered, full-thickness anastomosis is created with interrupted, monofilament absorbable sutures (Fig. 22.6).

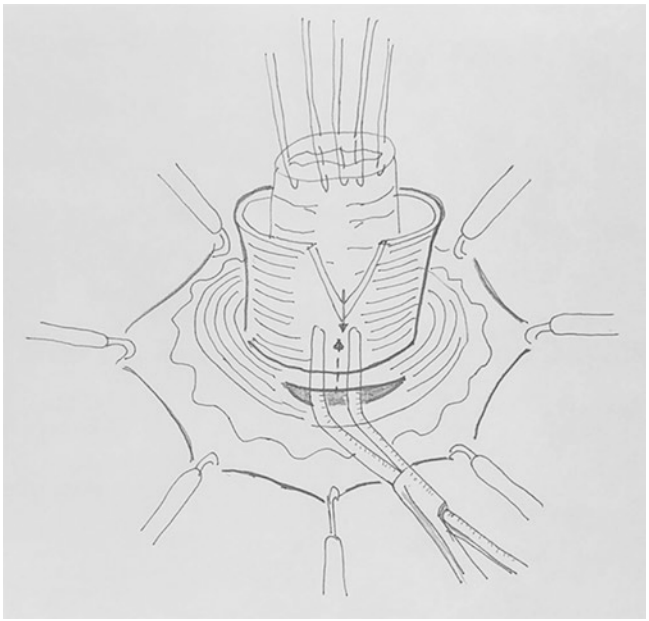

Fig. 22.5 Splitting muscle sleeve posteriorly down to the level of the proposed anastomosis

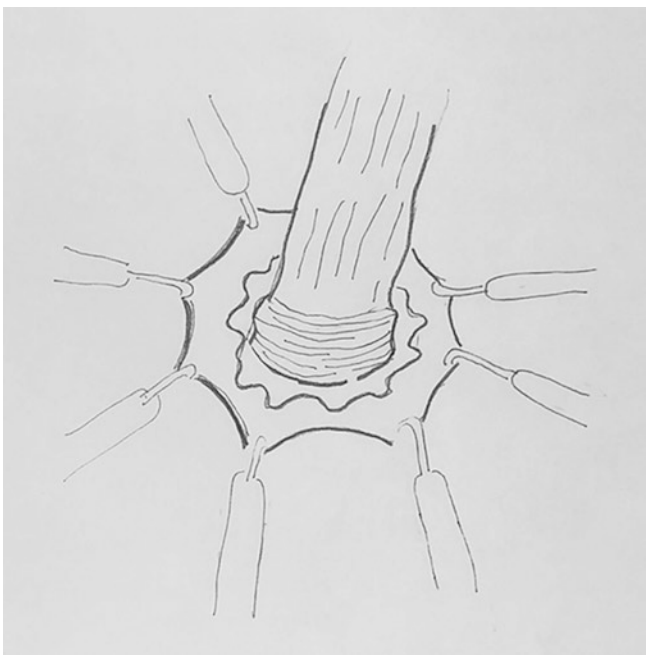

Fig. 22.4 Leaving the muscular cuff intact until the peritoneal reflection

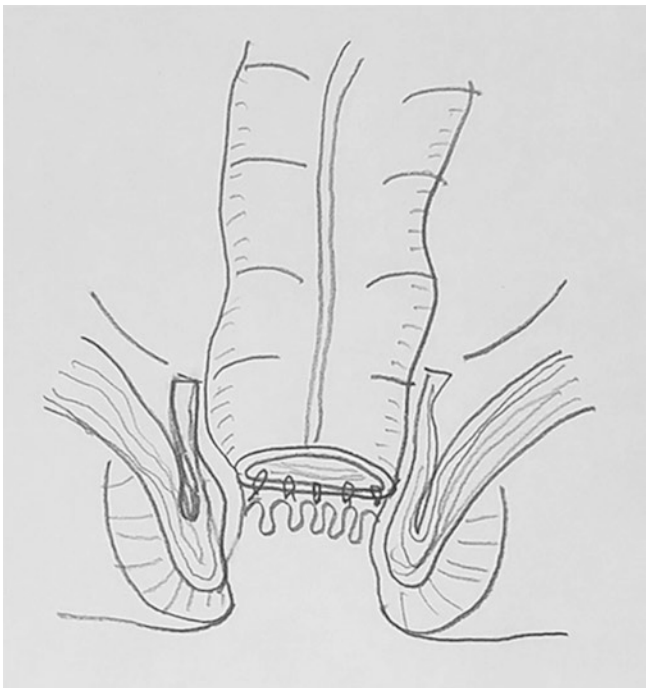

Fig. 22.6 Securing neoretum to anorectal cuff

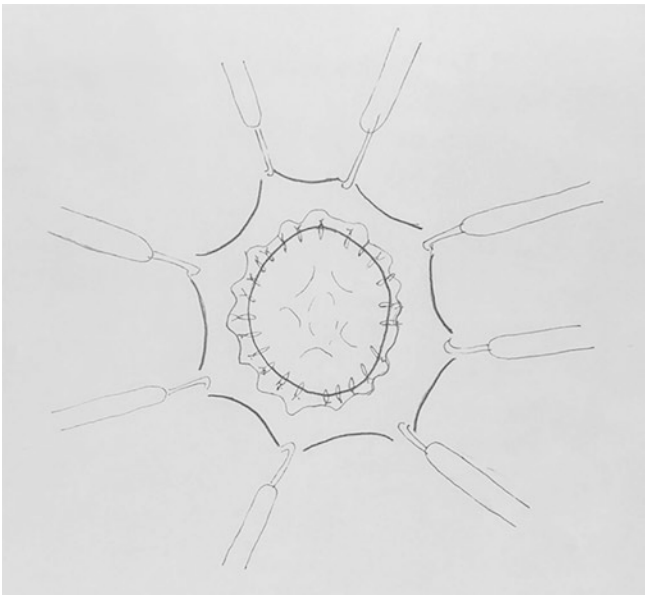

Fig. 22.7 The anastomosis is completed with a single layer of 5-0 PDSII sutures

The sutures should include a generous bite of the pull-through colon, as well as substantial bite of the underlying muscle and a small bite of the distal mucosa. Once again, care must be taken not to include the dentate line in the sutures, as this will produce more pain and may compromise later continence (Fig. 22.7).

For children with a transitional zone that is more proximal than the midsigmoid colon, there is usually not enough length to bring it down without some mobilization of at least the descending colon and in some cases the splenic flexure. This can be done either laparoscopically or trans-umbilical approach.

22.3 Postoperative Care

Intestinal activity is usually normal after a transanal pull-through procedure, and most infants have bowel movements during the first 24 h after surgery. Oral feeding can be started as soon as the child starts to pass stools, assuming that the abdomen is not distended. Oral acetaminophen is sufficient for postoperative pain in most cases.

Almost 50% of children develop perianal dermatitis (skin rash) because of frequent bowel movements and liquid discharge during the initial months after a transanal pull-through operation. It is important to prevent this as much as possible by immediate application of barrier creams. Both the frequency of stools and the perineal excoriation usually settle down within several weeks to months postoperatively.

There is a controversy about the need for daily rectal dilatations after a transanal pull-through procedure. Most surgeons wait 1–2 weeks and then calibrate the anastomosis with a Hegar dilator. Some then teach the parents to do daily dilatations for a maximum of 6 months postoperatively. Others proceed to daily dilatations only if there is evidence of anastomotic or cuff narrowing.

All children with Hirschsprung's disease are at risk for postoperative incontinence, enterocolitis, and obstructive symptoms, regardless of which operation is performed. Every child should therefore be followed up on a regular basis until at least the age of 5 years or longer if they are still having problems at that point. The management of incontinence and enterocolitis is dealt with in other contributions in this issue; this section will outline the investigation and management of the child who has persistent obstructive symptoms after a transanal pull-through procedure.

The most important and dangerous complication after a pull-through procedure is enterocolitis, because it is the most common cause of death in children with Hirschsprung's disease.

It is extremely important that the parents be educated as to the signs and symptoms of enterocolitis and that they bring the child to medical attention early if any of those clinical features occur.

Many preventive measures have been described, including routine postoperative irrigations or rectal stimulation, the use of antibiotics, and the use of probiotics.

22.4 Knack and Pitfalls of Transanal Endorectal Pull-Through

1. Age at pull-through

   Some surgeons prefer to wait until the child is a few months old before doing the procedure. The child is discharged home on rectal stimulation and/or rectal irrigations while waiting. There are several expressed reasons for this, such as a feeling that the operation will be easier with better visualization and a hope that the dilated proximal colon will decrease in size. The primary danger of this approach is the possibility of the child developing enterocolitis during the waiting period.

   Many pediatric surgeons have now realized that the transanal pull-through can be successfully and safely performed as soon as the diagnosis is made, even in small newborns. The success of the procedure lies in magnification with loupes, meticulous dissection, and the fact that the neonatal pelvis is very shallow.

2. How high above dentate line should the dissection start

   As a basic principle, the anastomosis must be high enough above the dentate line so that normal sensation is not interfered with. The age and size of the child are also a factor, with most surgeons starting the dissection somewhat higher in older children than in neonates. Most opinions range from 5 to 10 mm above the dentate line in a newborn and early infants.
3. Length of the rectal cuff

   In the original descriptions of the transanal pull-through procedure, the mucosal dissection was carried to a point above the peritoneal reflection, to ensure that there was no injury to pelvic structures. A short mucosal dissection is done for 1.0–3.0 cm, and the rectal wall is then incised circumferentially.

   The advantage of leaving a short cuff or no cuff is the avoidance of a constricting ring or residual aganglionic bowel, with a lower risk of obstruction and enterocolitis. The disadvantage is that dissection on the outside of the rectum deep in the pelvis may increase the risk of injury to pelvic nerves and vessels and to the prostate, urethra, or vagina.
4. How much of the ganglionated bowel should be resected

   Often the ganglionated bowel is grossly dilated or thickened, and some surgeons choose to resect it back to more normal appearing bowel. This decision is based on that dilated bowel does not have normal motility and will not function as well as the bowel that has a more normal caliber. Resecting some of the bowel proximal to the positive biopsy therefore ensures that the transition zone will not be used in the anastomosis. Recommendations range from 4 to 6 cm above the normal biopsy.

22.5 Conclusions

Transanal endorectal pull-through in neonatal patients is as feasible and safe as in older children or in those with a leveling colostomy. However, temporary postoperative skin rash occurs more frequently in neonatal patients, and postoperative dilatations are required more often than in older children.

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Rectoplasty with a Posterior Triangular Colonic Flap

23

Masaki Nio

23.1 Background

The surgical treatment of Hirschsprung's disease started with Swenson procedure [1], followed by Soave [2] and Duhamel procedures [3]. Many institutions have employed these three procedures and their modifications, including laparoscopic procedures.

The surgical outcome in terms of postoperative survival has been generally good; however, postoperative morbidities such as constipation and incontinence are still occasionally encountered. In such cases, morbidity is presumably due to a residual aganglionic segment that causes anal sphincter achalasia or damage to the sensation of defecation. There is a dilemma about whether complete release of anal achalasia or preservation of the sense of defecation in the anal canal should be performed. The decision regarding the level of anastomosis between the pulled-through intestine and anorectum seems to be essential to reduce postoperative morbidity. On the other hand, there is no objective standard to decide the level of anastomosis, because the distribution of the sensory nerves of the anorectum might not be the same among individuals, and the optimal level might be different during the Swenson, Duhamel, and Soave procedures and their modifications. Rectoplasty with a posterior triangular colonic flap (RPTCF) [4] has offered a resolution to this critical issue.

23.2 The Concept of RPTCF

During any procedure for Hirschsprung's disease, the dentate line is an important surgical landmark. However, the level of anastomosis between the normoganglionic intestine and anorectum is still being determined. While some surgeons recommended that anastomosis should be performed on the level of the dentate line, others recommended that it should be performed above the dentate line. Most surgeons realized that the level of anastomosis is related to the incidence of postoperative morbidities such as constipation and incontinence. If anastomosis is performed above and away from the dentate line, the patient is likely to suffer from constipation due to anal sphincter achalasia. However, if anastomosis is performed too low and close to the level of the anal skin, the patient is likely to develop incontinence due to loss of the sense of defecation.

Recently, preservation of the mucosa near the dentate line is preferred to avoid incontinence, which affects the patient's quality of life (QOL) more seriously than constipation. However, the optimal level is still uncertain.

Kasai et al. reported that RPTCF [4] can be used to solve these problems. These authors reported performing rectal myotomy with colectomy [5] based on the idea that rectal myotomy is useful to avoid damage to rectal sensation. Furthermore, they modified this surgery and reported an RPTCF procedure that could completely release anal achalasia and well protect the sense of defecation (Figs. 23.1, 23.2, 23.3, and 23.4). RPTCF is a modification of the Duhamel procedure. In this procedure, the anal canal is circumferentially preserved, except for at the 6 o'clock position, where a vertical incision is made across the dentate line. In addition, the internal sphincter muscle, which was halfway incised in the original report, is currently totally divided vertically (Fig. 23.2a). The external anal sphincter that is exposed in the anal canal is covered by the anal end of the pulled-through intestine, which is sutured to the anoderm and forms a triangular flap (Fig. 23.2b).

Currently, the Soave procedure with a transanal approach is widely employed to treat classic-type Hirschsprung's disease, because this surgery, which does not require laparotomy, is regarded as less invasive than others. We recently employed an additional rectoanal myotomy with the transanal Soave procedure, transanal endorectal pull-through with rectoanal myotomy (TEPTRAM).

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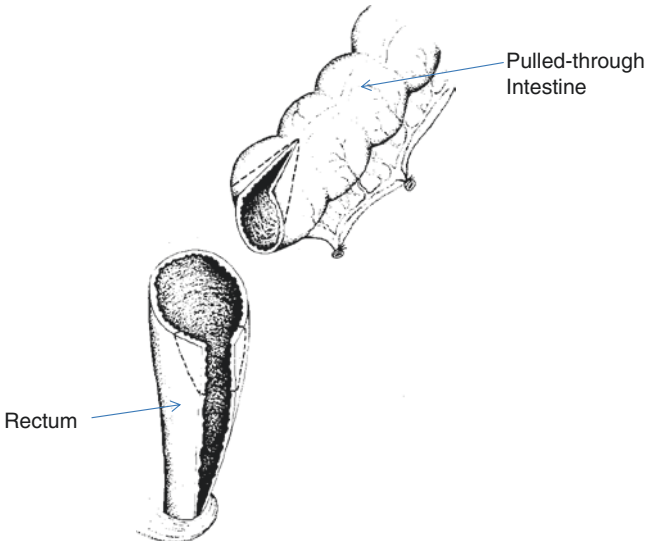

Fig. 23.1 Colorectal anastomosis. The posterior wall of the rectum is split in the midline. The colon is split along its taenia libera, and the anastomosis is performed between them

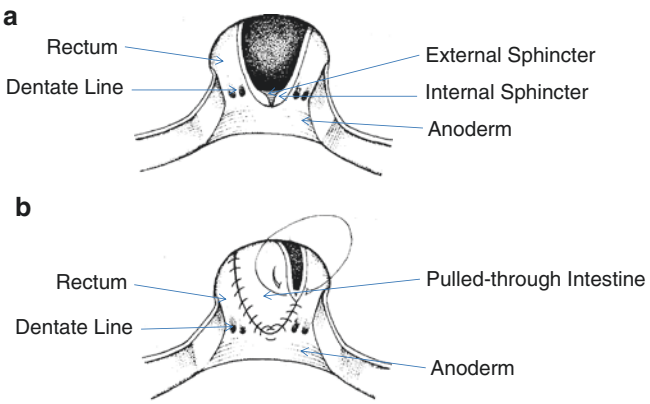

Fig. 23.2 Lower part of colorectal anastomosis. The incision of the posterior wall of the rectum is extended through the dentate line (**a**). The triangular colonic flap is pulled down through the rectum, and the colorectal anastomosis is performed (**b**)

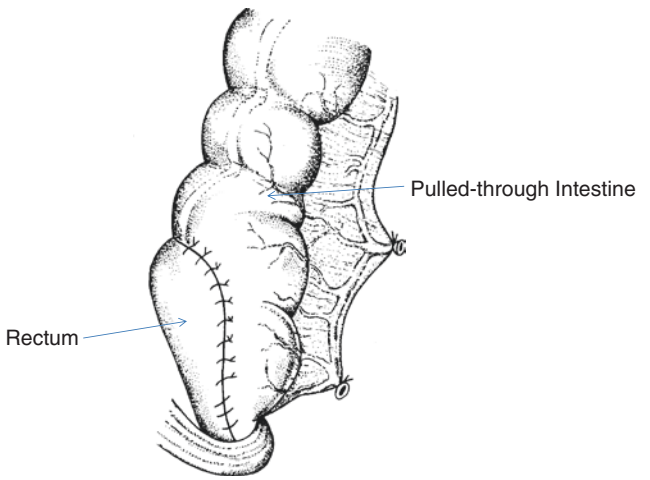

Fig. 23.3 Completion of colorectal anastomosis. The colorectal anastomosis is performed paying attention not to shape the rectal stump into a pouch

23.3 Surgery and Pre- and Postoperative Management

23.3.1 RPTCF

1. Preoperative preparation

   The preoperative preparation for RPTCF is almost the same as that for the Duhamel procedure. The colon and rectum should be well evacuated before the surgery. Previously, a stoma was created preoperatively. Currently, the primary surgery can be performed without the need for a stoma, and complete evacuation is guaranteed with enemas and lavage using a catheter.

   Previously, the timing of the surgery was late infancy, when the patient's body weight was 8–10 kg, because a hand-sewn anastomosis was employed at first. Currently, an endoscopic surgical stapler is available, and the surgery can be performed in early infancy, when the anal canal can accommodate the surgeon's index finger.

   During the neonatal period, diagnostic modalities such as a manometric study in which the rectoanal reflex is evaluated and rectal mucosal biopsy are sometimes unreliable. Thus, even when Hirschsprung's disease is suspected in a neonate, a pathological evaluation of a rectal mucosal biopsy cannot always reveal proliferation of acetylcholinesterase staining-positive nerve fibers. Then, the surgery is usually performed when the patient is 2 or 3 months old. In most cases, surgery can be delayed by 1–2 months using conservative treatment with enemas and/or colonic irrigation, in which a catheter is inserted into the colon.

   If the patient has a very long intestinal aganglionic segment such as total colonic aganglionosis, bowel evacuation using a catheter is sometimes difficult in early infancy. In this case, a stoma is created in the normoganglionic intestine, which is confirmed with frozen sections. Then, after confirming that the stoma works well, the surgeon can plan to perform staged corrective surgery. If the stoma is created at the umbilical site or lower abdomen, the stoma wound can be used during RPTCF.

2. Surgical techniques

   The surgery is performed with the patient under general endotracheal anesthesia and in the supine position. The area of the body from the abdomen to the legs is disinfected, and both legs are wrapped in sheets. The head and chest are also covered by sheets, and the abdominal and perineal areas are exposed to reveal the surgical field. A Foley balloon catheter is placed into the urinary bladder in the clean area.

   Laparotomy is performed using an infraumbilical or lower abdominal transverse incision. Laparoscopic surgery is another alternative. The caliber change of the

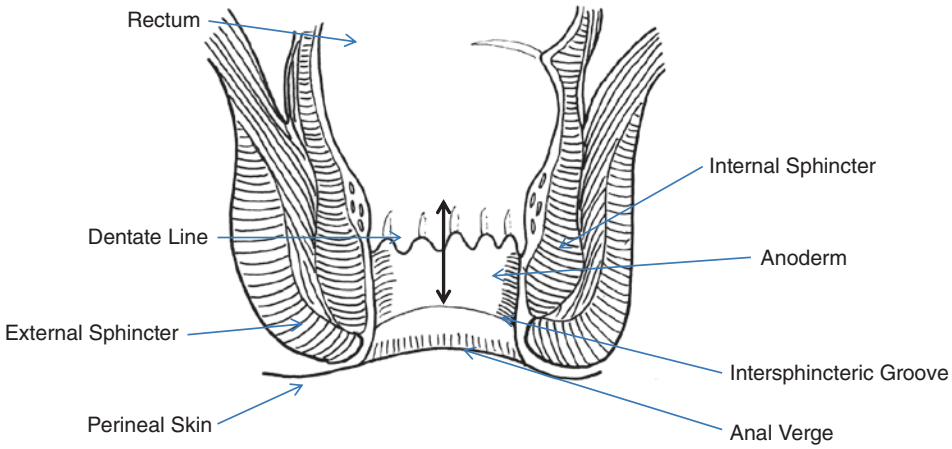

Fig. 23.4 The vertical myotomy of the internal anal sphincter. The internal sphincter muscle is vertically divided across the dentate line (↔)

intestine is confirmed, full-layer biopsies are taken from the oral and anal sides of the caliber change, and the aganglionic and normoganglionic areas are pathologically confirmed using frozen sections.

The surgeon determines the border of the oligo- and normoganglionic intestines, and the area between them is transected. Both stumps are closed provisionally.

The aganglionic intestine is dissected toward the pelvic cavity. The mesentery up to the peritoneal reflection is divided along the intestinal wall, and the peritoneal reflection is dissected and divided circumferentially around the rectum. Below this point, blunt dissection of the dorsal part of the rectum proceeds toward the pelvic floor. The blood vessels from both sides into the rectum are carefully preserved. The dissection reaches the pelvic floor, and the procedure of the abdominal side is suspended provisionally.

The surgery proceeds to the perineal side. In the lithotomy position after lifting both of the patient's legs, a self-retaining ring retractor is utilized, and the anal canal is exposed. After confirming the dentate line, the surgeon injects a small amount of saline into the submucosa at the 6 o'clock position. Then, the rectal mucosa and anoderm are vertically incised across the dentate line using an electrocautery device. After creating a shallow vertical incision and performing gentle dissection with mosquito forceps, the surgeon visualizes the internal sphincter muscle. This muscle is exfoliated little by little until the external sphincter muscle is sufficiently exposed. A nerve stimulator is utilized to verify the external sphincter muscle. The internal sphincter muscle does not contract due to the stimulus. If the first muscle contraction is recognized due to the stimulus, the appropriate plane has been reached, and the surgeon must refrain from performing further dissection.

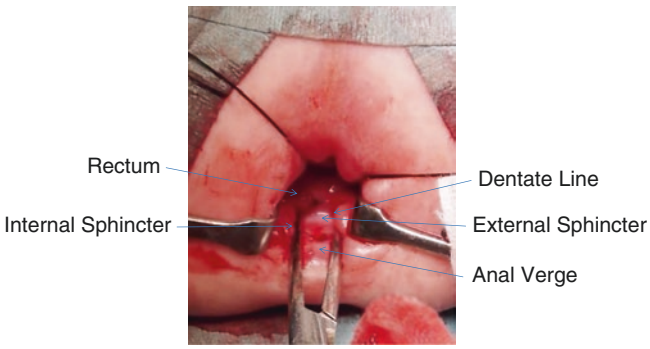

Fig. 23.5 The internal anal sphincter myotomy and the external sphincter. The external anal sphincter is exposed after finishing the internal sphincter myotomy

The internal sphincter muscle is vertically split using a triangular forceps and an electrocautery device toward the anal verge. The internal sphincter is completely and vertically divided at the 6 o'clock position (Figs. 23.4 and 23.5).

The lower part of the anoderm that overlies the anal end of the internal sphincter should be preserved. This is because an anastomosis should be made between the anoderm, not the perineal skin, and the pulled-through intestine. If the anastomosis is made with perineal skin, soiling might occur.

The dorsal side of the rectal wall is bluntly dissected upward to the pelvic cavity, and the dissected area is connected to the space at the pelvic floor that was created from the peritoneal side.

The size of the vertical incision of the rectal wall is adjusted according to the diameter of the pulled-through intestine. The route between the rectal orifice and peritoneal space is bluntly and appropriately enlarged using a Hegar dilator and the surgeon's finger. Then, the perineal side is prepared.

The surgery proceeds to the abdominal side again. The pulled-through intestine is prepared. If the pull-through appears to be difficult due to the lack of intestinal or vascular length, dissection is continued.

The surgeon might need to divide the main trunk of the ileocolic vessels to release the tension that is encountered due to the lack of vascular length. In this case, sufficient care should be taken to ensure that the blood flow is maintained via the marginal arcade of the mesentery.

In case the hepatic flexure is dissected, the right colon and terminal ileum must be flipped to the right side and then pulled through to the perineum. If the right colon and terminal ileum that are pulled through medially rotate naturally, and are not flipped to the right side, the mesentery of the pulled-through intestine is twisted in the pelvis.

When the intestine to be pulled through is ready, a thick Penrose drain is introduced from the perineal side to the pelvic cavity. The end of the intestine, along with the mesentery, is wrapped in the Penrose drain, fixed to the drain with several stitches, and then gently and slowly pulled through with the drain to the perineal side. When the intestine is successfully pulled through to the perineum through the rectal orifice without tension or twisting, the Penrose drain is removed from the intestine.

The end of the intestine is trimmed for anastomosis. Using a 5–0 PDS II, the surgeon makes an end-to-side anastomosis between the pulled-through intestine and rectum with interrupted sutures. Following anastomosis, side-to-side anastomosis is performed between the pulled-through intestine and rectum using a surgical stapler. Before applying the stapler, the surgeon places two stitches at the 1 o'clock and 11 o'clock positions of the pulled-through intestine (5 o'clock and 7 o'clock positions of the anastomosed rectum). After pulling these sutures, the surgeon inserts the stapler, placing one jaw into the pulled-through intestine and the other jaw into the rectum. After confirming that no surrounding tissue or organs interfere between the jaws of the stapler, the surgeon staples from the perineal side. One more staple is applied in the same way, if needed. The oral stump of the rectum is opened, trimmed, and closed by suturing the rectum and intestinal window, which is made at the oral end of the anastomosis according to the size of the rectal end.

In this step, care should be taken to avoid forming the rectal stump into a pouch. The pelvic cavity is irrigated with a sufficient amount of warm saline. The peritoneum is repaired, a closed drain is placed in the pelvic floor, and the abdominal wound is closed.

3. Postoperative management

The postoperative management is the same as for the usual abdominal surgeries. The drain is removed when defecation is initiated, and oral intake is started without any signs of complications such as postoperative bleeding or infection. A finger bougie is started 2 weeks postoperatively. The surgeon slowly advances his or her index finger into the rectum. The bilateral suture lines are felt, and they merge at the top of the anastomosis. The edge of the top of the anastomosis is gently pushed with the tip of a finger, taking care to avoid creating a prominent ridge at the edge, which may lead the rectal stump to form a pouch-like structure. The finger bougie is performed every day in the same way and continued by the patient's family for several months.

23.3.2 TEPTRAM

1. Preoperative preparation

The preoperative preparation for TEPTRAM is basically the same as for RPTCF. Because a surgical stapler is not used in this procedure, the size of the anal canal does not matter, and earlier surgery might be possible. However, patients usually undergo this surgery after the neonatal period. This is due to the difficulty of accurately diagnosing the condition of neonates, as mentioned before. Neonates also have a risk of damage that is related to early surgery to the fragile muscular tissue around the lower rectum and anal canal.

2. Surgical techniques

Basically, the procedure is almost the same as the transanal Soave procedure. Transanal mucosectomy begins at the rectum, more than 5 mm away from the upper margin of the surgical anal canal (Herrmann' line). Mucosectomy is advanced toward the pelvis. The muscle cuff is sufficiently prolapsed toward the anal canal, the cuff is incised at the 12 o'clock position, and the peritoneal cavity is entered. The muscular cuff is circumferentially divided. The mesentery is dissected, and the rectum and sigmoid colon are gradually extracted from the anus. Aganglionosis is diagnosed using frozen sections of full-layer specimens that are taken from the oral and anal sides of the caliber change. Then, myotomy of the internal sphincter is performed in the same manner as RPTCF. The muscle layer of the lower rectum is already exposed during mucosectomy. The distal ends of the rectal mucosa and anoderm are vertically incised at the 6 o'clock position across the dentate line using an electrocautery device. The internal sphincter muscle, which is located in the

same layer as the rectal muscle, is exposed. The internal sphincter muscle is then vertically divided until the external sphincter muscle is exposed. Muscle contractions are repeatedly checked during this procedure using a nerve stimulator. After finishing myotomy of the internal sphincter, the surgeon completely divides the muscular cuff of the rectum at the 6 o'clock position in the pelvic cavity using an electrocautery device.

An anastomosis is made between the pulled-through normoganglionic intestine and the end of the rectum above the surgical anal canal and anoderm, partly at the 6 o'clock position. The surgical anal canal must not be involved in the anastomosis except for at the 6 o'clock position. Furthermore, the exposed external anal sphincter is patched using the posterior wall of the pulled-through normoganglionic intestine, which forms a small triangular flap. The anal verge, where the anoderm transitions to the perineal skin, should also remain intact circumferentially.

3. Postoperative management

Patients who undergo TEPTRAM require more careful postoperative management than those with RPTCF. In this procedure, the muscular cuff remains; thus, postoperative contraction always occurs due to scarring around the muscular cuff. The surgeon performs bougie using his or her index finger, starting at 2 weeks postoperatively. Initially, the finger bougie is performed very gently, taking care not to damage the suture line. It is important to sufficiently dilate the full range of the muscular cuff. The patient's family continues performing the bougie technique daily for at least several months after RPTCF.

In our institution, we employ TEPTRAM for patients with classic-type intestinal aganglionosis. TEPTRAM can only be performed with the transanal approach, without the need for an abdominal procedure, and this procedure is less invasive than others. If a patient has a longer aganglionic segment than those with the classic type and requires abdominal surgery, RPTCF is usually indicated.

In RPTCF, mucosectomy is not required, and the operative time is shorter than for TEPTRAM in creating the pull-through route in the pelvis. More importantly, the aganglionic rectum is expected to play a role in the absorption of water and electrolytes, functioning as a reservoir; and this role is more important in total colonic and extensive intestinal aganglionosis. Postoperative care is very important for patients with RPTCF and TEPTRAM. If the patient has a dilated, pulled-through intestine, bowel evacuation during bowel movements is usually facilitated by the combination of enemas and suppositories. Bowel irrigation might be required in severe cases. Probiotics are routinely administered, and laxatives are used as needed. Postoperative management to overcome incomplete fecal evacuation after defecation is strongly recommended.

The best management during the first 2–3 years postoperatively is required to achieve long-term, good QOL in these patients.

23.4 Conclusions

The surgical techniques and postoperative management of patients who undergo RPTCF and TEPTRAM were described in this chapter. In both types of surgeries, the surgical anal canal is circumferentially preserved, except for at the 6 o'clock position, to maintain the sense of defecation. Furthermore, at the 6 o'clock position of the anal canal, the internal sphincter muscle is completely and vertically divided to avoid anal sphincter achalasia. RPTCF is likely to lead to a high level of patient satisfaction in terms of bowel function if the surgery and postoperative management are performed adequately. The most important part of this procedure is how to divide the internal anal sphincter. The use of a nerve stimulator is essential.

TEPTRAM is a modified transanal Soave procedure, and rectoanal myotomy is added following the concept of RPTCF. The advantage of this procedure is that abdominal surgery is not required; however, more careful postoperative management is required due to a residual muscular cuff. With correct surgical techniques and the best postoperative care, the functional outcome of TEPTRAM is expected to be similar to that of RPTCF.

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Laparoscopic Operation

24

Atsuyuki Yamataka, Masahiro Takeda, and Go Miyano

24.1 Introduction

Surgical cure of HD involves removing the aganglionic bowel segment and reconstructing the intestinal tract by bringing normally innervated bowel down to the anus while preserving the sphincter mechanism and sensory innervation of the ATZ to ensure good POBF.

In 1995, successful primary laparoscopic endorectal pull-through with transanal mucosectomy (i.e., L-TAPT) was described by Georgeson et al. [1], and subsequently, in 1998, De La Torre-Mondragon reported a single-stage transanal endorectal pull-through [2]. Since then, the efficacy and safety of this pure TAPT procedure have been reported [3, 4], and most centers will opt to treat HD using either minimally invasive surgical (MIS) techniques (i.e., L-TAPT) or pure TAPT.

Here, the surgical cure of short-type HD using MIS techniques will be described, focusing on a modified L-TAPT procedure developed specifically by the authors.

24.2 Preparing for Surgery

The authors' L-TAPT is a modification of Georgeson's classic procedure [1] and De La Torre-Mondragon's procedure [2]. The most distinct features are the level at which transanal dissection is commenced, in other words, the ARL, which represents the squamous columnar junction of the ATZ and is readily visible in viable tissue, and the length of the residual rectal muscle cuff [5].

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24.2.1 Contraindications to MIS

MIS is generally contraindicated in HD patients if there is a history of previous abdominal surgery (other than stoma surgery), severe enterocolitis, or the presence of any coexisting condition that may deteriorate during pneumoperitoneum. When rectosigmoid dilatation is extreme, an ileostomy or colostomy should be considered to reduce risks for complications, such as wound infection and abscess formation or stenosis at the coloanal anastomosis.

24.2.2 Preoperative Preparation for L-TAPT

Intensive preoperative bowel preparation is mandatory for L-TAPT. Patients without stomas may continue normal oral intake until 2–3 days before surgery. Parents familiar with glycerin enema administration may use daily glycerin enemas with or without bowel irrigation with normal saline to decompress the colorectum. Once admitted to hospital, oral intake is limited to clear fluids only, and intravenous fluid replacement is commenced. Bowel irrigations with normal saline are performed twice daily, and magnesium citrate is administered (1 g/kg) until there is no fecal residue forthcoming. An aminoglycoside antibiotic (100 mg/kg/day) is given orally the day before surgery. Broad-spectrum antibiotics such as ceftazidime (120 mg/kg/day) and isepamicin sulfate (8 mg/kg/day) are given intravenously once the patient is fully anesthetized.

Peripheral intravenous nutrition including amino acid and intravenous fat emulsion supplementation is highly recommended because in total, the period a patient will be nil by mouth both pre- and postoperatively will generally be 4 days. If necessary, more intensively managed nutritional support may be considered using intravenous hyperalimentation through a central venous catheter.

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24.2.3 Patient Positioning

After induction of general endotracheal tube anesthesia, the patient is positioned at the end of the operating table in the supine position. The patient's body is disinfected. For infants, the trunk and buttocks are prepared extensively, then the legs circumferentially to the tips of the toes, and sterile stockings are placed on both legs. The legs are raised when transanal dissection is commenced. Children older than infants are positioned in the lithotomy position with their legs in stirrups.

The laparoscopic surgeon and the scopist stand on the patient's right side. The scrub nurse stands at the left lower end of the Table. A monitor is positioned beyond the patient's feet. The table is placed head-down for both laparoscopic colorectal dissection and transanal dissection. A urinary catheter is used to decompress the bladder.

24.3 Surgical Technique

24.3.1 Step One: Trocar Placement

A 5 mm port is inserted through the umbilicus using an open Hasson technique, and pneumoperitoneum is established with carbon dioxide to a pressure of 8–10 mmHg. Three additional 3 or 5 mm ports are placed in the right upper and lower quadrants and in the left upper quadrant, respectively. A laparoscope is inserted through the 5 mm port in the right upper quadrant. The surgeon's two working ports are the umbilical port for the left hand and the right lower abdominal port for the right hand. The port in the left upper abdomen can be used for either retraction of the colon or additionally for the surgeon's left hand.

24.3.2 Step Two: Laparoscopy-Assisted Colon Suction Biopsy

Laparoscopy-assisted colon suction biopsy can be performed in any infant or child of any size with rectosigmoid type HD, because the sigmoid colon can be mobilized readily to allow the tip of the suction biopsy device to reach the proposed biopsy site. Fortuitously, 80% of HD cases are rectosigmoid, and laparoscopic-assisted colon suction biopsy is safe, simple, and quick compared with full-thickness biopsy.

After identification of the region of caliber change in the colon laparoscopically by a surgeon from the laparoscopy team, the suction biopsy device is inserted into the anus from the transanal pull-through team (Fig. 24.1) ensuring that the tissue sampling mechanism to check for any possible risks for perforation. After the suction biopsy, the laparoscopic surgeon places a metal laparoscopic vessel clip at the biopsy site as a marker. Biopsy specimens are sent for immediate assessment by a pathologist. If the result is aganglionic, the biopsy is repeated more proximally. If ganglion cells are present, the colon is pulled through to the level of the clip transanally, and a coloanal anastomosis is performed. Before the anastomosis is performed, full-thickness biopsies are taken at 12, 3, 6, and 9 o'clock circumferentially at the level of the clipped biopsy site that has been exposed through the anus.

24.3.3 Step Three: Laparoscopic Colorectal Dissection

If the biopsy site is ganglionic, the laparoscopic surgeon starts dissection of the colorectum. Mesenteric vessels are divided distal to the level of the clipped biopsy site, leaving

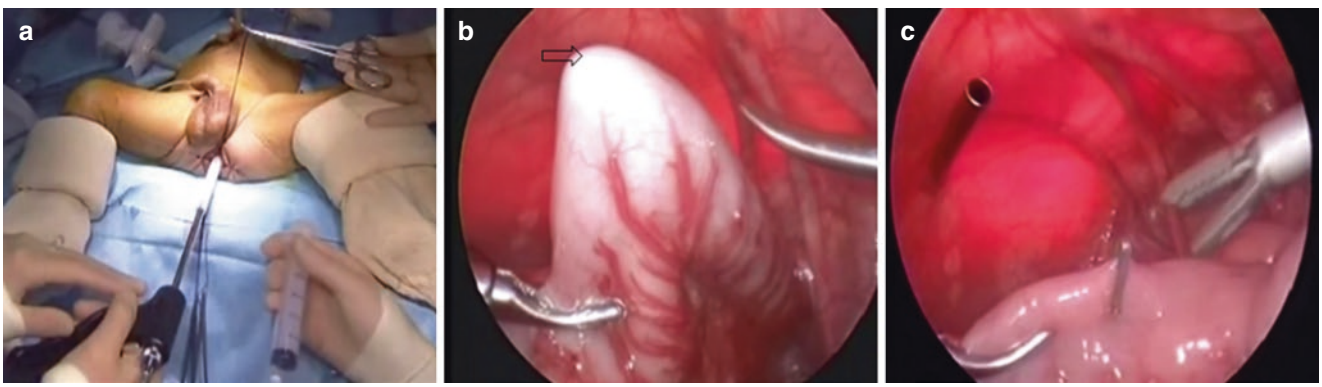

Fig. 24.1 A suction rectal biopsy device is being advanced (**a**) into the colon through the anus by a surgeon from the transanal pull-through team under the supervision of a laparoscopic surgeon until the tip (**b**, open arrow) of the device lies proximal to the region of caliber change. The surgeon places a metal laparoscopic vessel clip at the biopsy site as a marker (**c**)

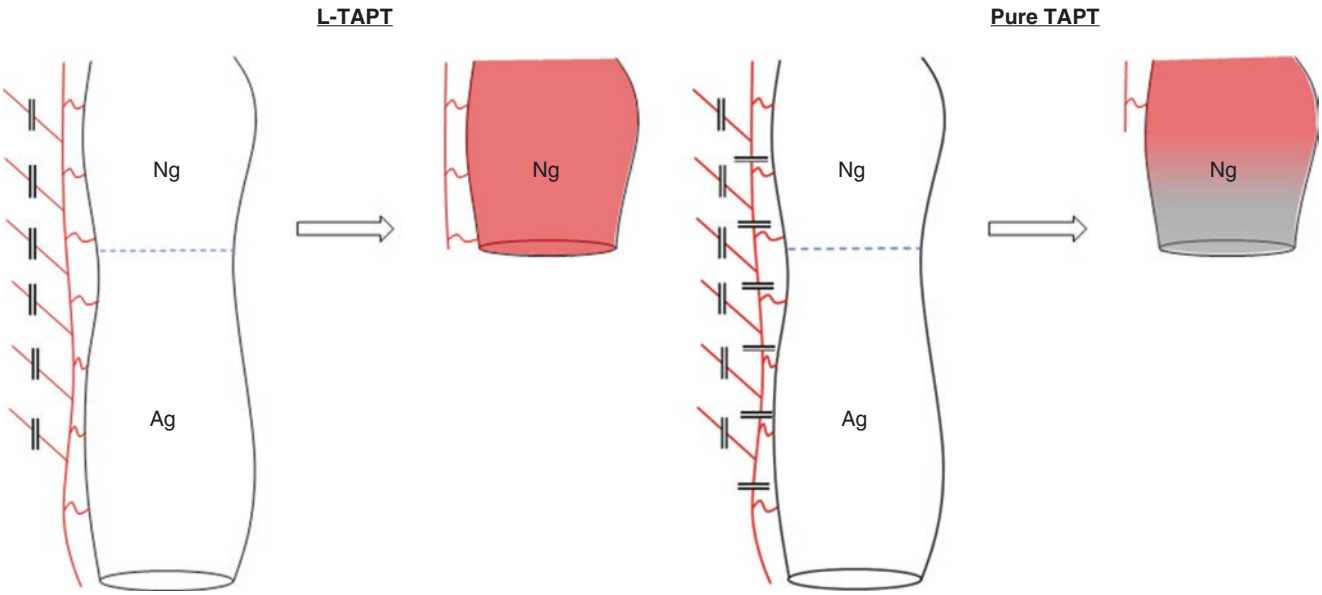

Fig. 24.2 A significant advantage of L-TAPT is the ability to mobilize the colon while keeping marginal arteries intact, unlike during TAPT without laparoscopic coloanal dissection (pure TAPT) where marginal arteries to the pull-through colon be sacrificed. Short double lines indicate ligation sites. *Ng* normoganglionic; *Ag* aganglionic

both the marginal artery and vein intact at the level of the clipped biopsy site. Then, the mesenteric vascular arcade proximal to the clipped biopsy site is inspected, and vessels are divided to allow the pull-through colon to reach the anus without tension. Thus, marginal vessels in the pull-through colon are essentially intact, ensuring good vascular perfusion even in the distal end of the pull-through colon. Further dissection is continued in the rectum distal to the peritoneal reflection circumferentially, which greatly facilitates invagination of the proximal colorectum into the distal rectum during transanal rectal dissection. The laparoscopic surgeon should identify the location of the ureters and vas deferens (in males) for dissection of the distal rectum. Another important point is that dissection of the mesorectum should follow the rectal wall as closely as possible to avoid injuring the hypogastric nerve which is related to ejaculation and the pelvic splanchnic nerve which is related to erection and excretory function.

A significant advantage of L-TAPT is that the colon can be mobilized keeping the marginal arteries at the distal end of the pull-through colon intact to ensure good blood supply to the coloanal anastomosis. In contrast, without laparoscopy, marginal arteries are likely to be injured or sacrificed (Fig. 24.2).

24.3.4 Step Four: Transanal Dissection

While awaiting histopathology results after colon suction biopsy, the patient is placed in the lithotomy position by flexing the patient's legs, and the perineal surgeon places 3–0 traction sutures circumferentially 3–4 cm from the anus to expose the DL. These traction sutures play a vital role for ensuring that a Lone Star Ring Retractor System (Lone Star Medical Products, Inc., Stafford, TX) can be attached correctly to expose and confirm the ARL. The anal valves along the DL at the bottom of the anal sinuses are then hooked up using the Lone Star Ring Retractor System allowing the ARL to be identified as a ring at the top of the anal columns of Morgagni (Fig. 24.3) [6]. By omitting these traction sutures or not placing them correctly, the anal valves along the DL will not be exposed adequately, and it is most likely that the Lone Star Ring Retractor will be hooked to the anal verge rather than the DL. When retracted circumferentially, both the DL and ARL will not be retracted toward the anus, and the surgeon will not be able to see the ARL under direct vision.

Multiple fine traction sutures are placed proximal to the ARL, and the mucosa is incised just proximal to the ARL circumferentially using needle-tipped electrocautery. The ARL and ATZ are left intact (Fig. 24.3). The perineal surgeon commences near full-thickness rectal dissection transanally progressing cranially for about 10–15 mm in the plane of the rectal muscle layer, taking great care not to injure the external anal sphincter. A large bore silicon tube is inserted into the rectal lumen as a stent, and the plane of dissection is changed to the submucosal plane and continued proximally. As mucosectomy progresses further proximally, the rectosigmoid colon which has already been prepared laparoscopically for pull-through begins to invaginate into the rectal

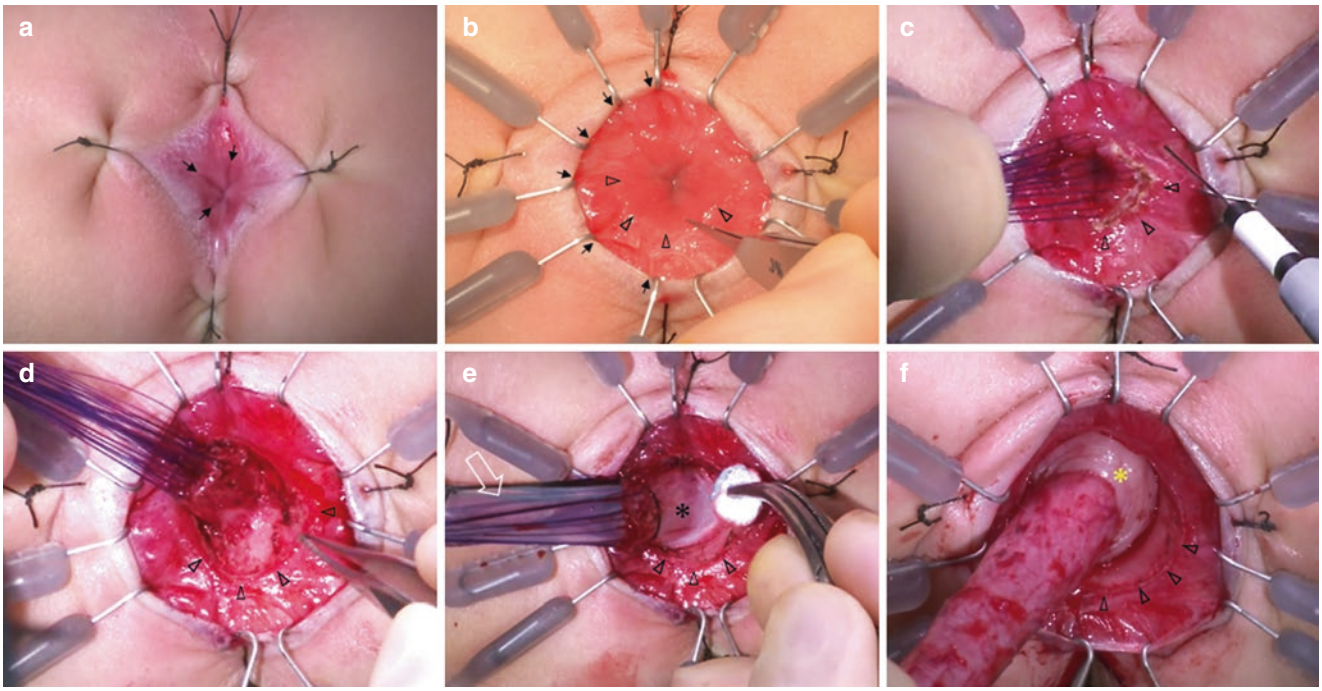

Fig. 24.3 3-0 traction sutures circumferentially 3–4 cm from the anus can expose the DL (arrows) (**a**). The ARL (arrowheads) can be identified by hooking the crypts (arrows) on the DL to expose the anal transitional zone with a ring retractor device (**b**). Note multiple fine traction sutures just proximal to the ARL (arrowheads) and the incision just proximal to the ARL (**c**), leaving the ARL (arrowheads) intact (**d**). A large bore silicon tube (large open arrow) has been inserted into the rectal lumen (**e**), to facilitate transanal "submucosal" (an asterisk) dissection. The rectosigmoid colon begins to invaginate into the rectal muscle cuff (a yellow asterisk) and eventually reaches the anus (**f**). When this invagination starts, submucosal dissection is considered to be adequate

muscle cuff and reaches the anus without any need for dividing the mesenteric vessels transanally. When this invagination starts, submucosal dissection is considered to be adequate, and the invaginated muscular wall of the rectum is divided circumferentially. The proximal rectosigmoid is delivered through the anus externally without applying tension until the proposed site for the coloanal anastomosis marked by the metal clip is identified.

Before the coloanal anastomosis, the pull-through colon is assessed for torsion laparoscopically (Fig. 24.4) and tension on both the pull-through colon and vasculature. If there is any tension, further laparoscopic dissection/mobilization is mandatory to prevent retraction of the pull-through colon that may cause leakage at the anastomosis that could lead to pelvic abscess formation.

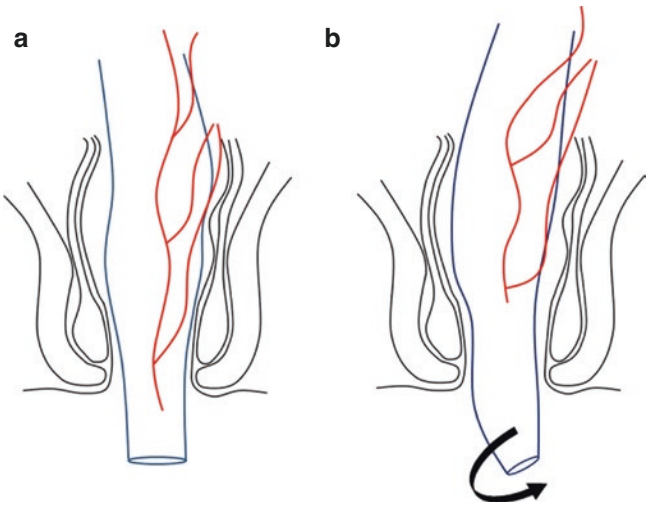

Fig. 24.4 When transanal dissection is performed, the pull-through colon (**a**) does not become torted if the mesentery (red) is of adequate length. If the mesentery is relatively shorter than the colon, the pull-through colon becomes torted (**b**). EAS, external anal sphincter

24.3.5 Step Five: Total Excision of the Posterior Aganglionic Rectal Muscle Cuff

Before the coloanal anastomosis, the aganglionic rectal cuff should be excised to eliminate any chance for complications caused by the residual cuff to occur. The rectal cuff is divided at the 3 and 9 o'clock positions into anterior and posterior cuffs. The anterior rectal cuff is then divided in the midline (12 o'clock) and then excised till where laparoscopic dissection was performed to, usually slightly distal to the peritoneal

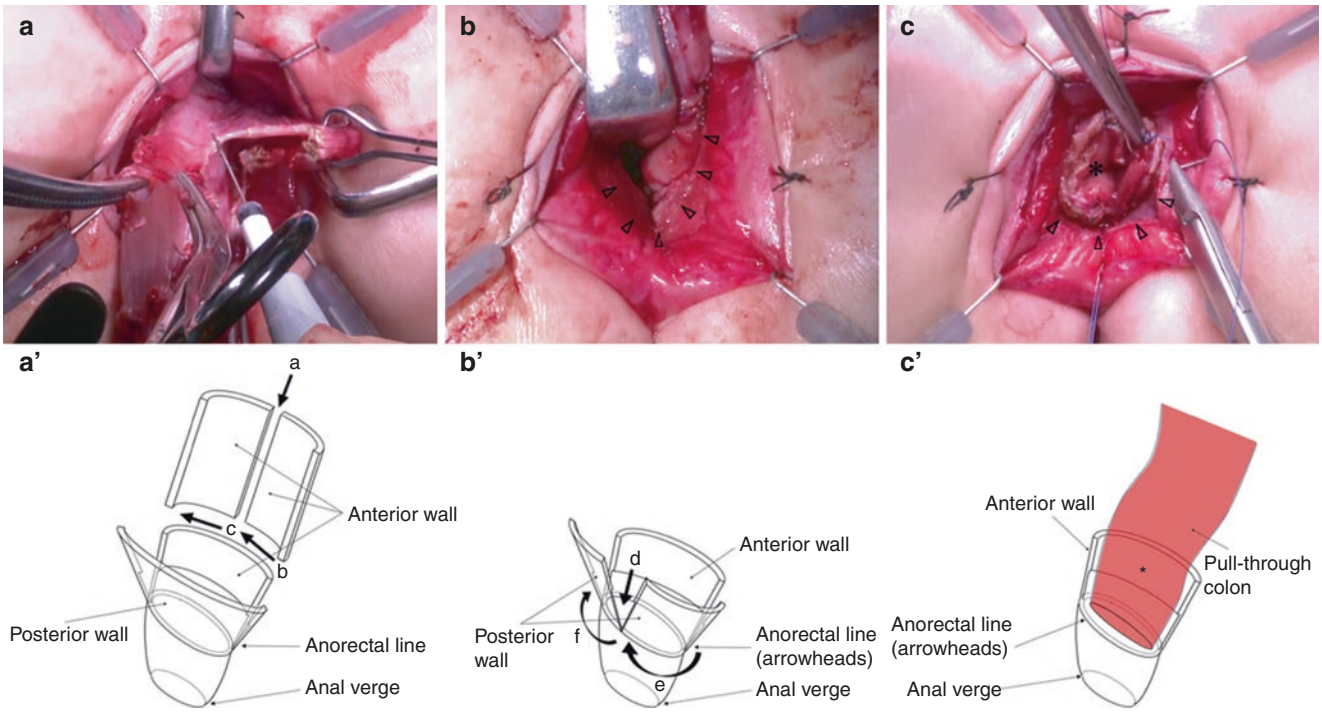

Fig. 24.5 The anterior rectal cuff is divided in the midline (12 o'clock) (**a**) and excised to the point where the laparoscopic dissection was performed (a–c). After "d", "e," and "f" in **b**′, the entire posterior aganglionic rectal cuff is removed while preserving the ARL completely (arrowheads) (**b**). The pull-through colon (asterisk) being anastomosed to the ARL (arrowheads) using interrupted sutures (**c**)

reflection (Fig. 24.5). The distal anterior cuff is excised leaving the proximal anterior cuff intact to prevent injury to nerves supplying the urinary tract. The posterior rectal cuff is then divided caudally in the midline (6 o'clock) down to where the mucosectomy was commenced (some 10–15 mm proximal to the ARL) to ensure that achalasia due to aganglionic rectum and structural muscle ring is released completely. In other words, since the first 10–15 mm of rectal dissection from the ARL is nearly in full thickness, the entire posterior aganglionic rectal cuff is removed.

The pull-through colon is anastomosed just above the ARL using interrupted absorbable sutures.

24.4 Postoperative Care

Provided L-TAPT is performed meticulously without any intra- or postoperative complications; recovery is expected to be unremarkable with routine postoperative care. Intravenous fluids and nasogastric decompression are continued postoperatively until bowel function returns. The urinary catheter is left in place until the next morning. When bowel function returns, oral intake is initiated with tapering of intravenous fluids, typically by 3–4 days postoperatively. Intravenous antibiotics are continued for 3 days postoperatively, and patients can be discharged once a full oral diet is tolerated.

24.5 Complications and Their Management

Complications after L-TAPT can be classified as either early or late. Early serious postoperative complications include anastomotic leakage, retraction of the pull-through colon, abscess formation at the coloanal anastomosis, or consequences of the pull-through of a transitional segment of colon, such as unstable bowel function. Late complications include intractable constipation, enterocolitis, bowel obstruction, incontinence, and anal stenosis/stricture.

One neonatal case of postoperative obstruction is caused by residual rectal cuffs that had only been split in the midline and had folded caudally toward the anus outside the pull-through colon while it was being pulled through down to the anus [7]. This patient required redo surgery to remove the rectal cuffs using a posterior sagittal approach. After experiencing this case, all posterior rectal cuffs are routinely excised in toto, because splitting the rectal cuff in the midline alone may cause postoperative obstruction.

24.6 Discussion

In 2017, Neuvonen et al. reported the long-term POBF and quality of life after TAPT (including pure TAPT and L-TAPT) in relation to controls selected from the general population [8].

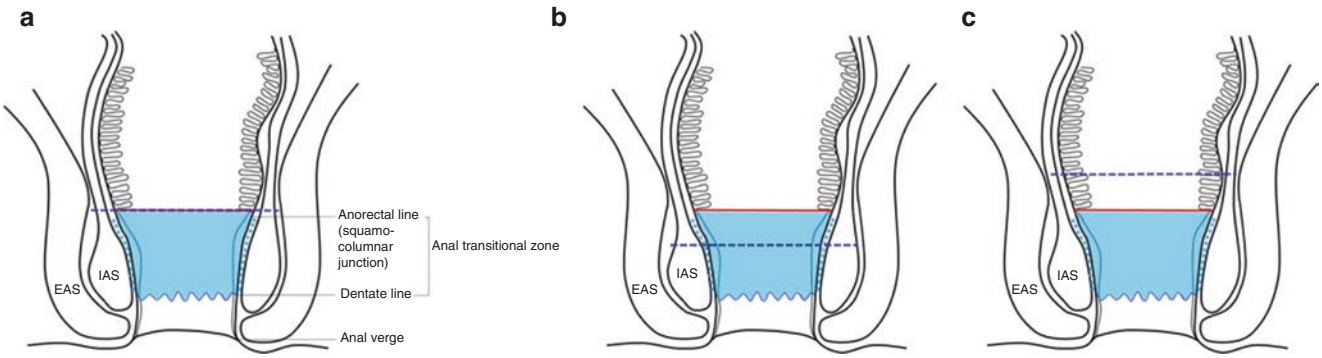

Fig. 24.6 Red solid lines indicate the ARL at the top of the anal columns, and blue wavy lines indicate the DL at the bottom of the anal sinuses. The ATZ is the light blue region between the ARL and the DL. The blue broken lines indicate where transanal dissection should start. When commenced just above the ARL (**a**), POBF will be more reliable and predictable because the ARL is a fixed landmark. However, if "above" the DL is too low (i.e., below the ARL, (**b**) the ATZ will be injured causing fecal incontinence, and if too high (i.e., above the ARL, (**c**), residual aganglionic rectum will cause constipation. *IAS* internal anal sphincter, *EAS* external anal sphincter

In this large series, only 75% of patients were socially continent after TAPT. While soiling and fecal accidents experienced during childhood improved with age to be comparable with controls by adulthood, the frequency of stooling remained higher in TAPT cases in adulthood. To improve and standardize post-TAPT (including pure TAPT and L-TAPT) bowel function, transanal dissection should commence just proximal to the ARL, leaving the ARL intact, and the posterior rectal cuff should be totally excised.

The DL is the traditional landmark used for the starting point of transanal dissection, with a range of flexibility of 5–20 mm [9] reported as acceptable because the recommendation is "above" the DL. As a consequence, the ATZ may be injured, or aganglionic mucosa may be left behind (i.e., if commenced too high, there is a tendency for constipation, and if commenced too low, there is a tendency for staining) (Fig. 24.6). The distance chosen above the DL would appear to be quite subjective, especially when the age and physique of a patient are also taken into account, with the result that postoperative outcome in patients where the DL is used as a landmark can be somewhat unpredictable. The ARL is a natural demarcation that can be located accurately in all patients irrespective of age, size, or build and that does not need any subjective interpretation in contrast to "above" the DL.

The modified L-TAPT technique described preserves the ATZ between the DL and the ARL, ensuring that the anorectum has normal sensory and motor function, preventing postoperative fecal staining/soiling. In fact, the authors' most recent research using HD model mice [10] found no apparent differences in sensory innervation of the ATZ, compared with normal mice, a proof of the importance of an intact ATZ in HD.

There are also reports about short residual cuff remnants being associated with improved short-term results in pure TAPT and L-TAPT cases [11], but from experience, complications related to residual cuffs cannot be resolved by merely leaving some aganglionic cuff behind, no matter how short. The most efficient way to stabilize POBF would be to standardize dissection and remove the cuff entirely. Should a residual cuff cause stricture then it must be removed by total excision. In Georgeson et al.'s 1995 report, they suggested splitting the residual cuff to the level of the proposed anastomosis [1]. Again, from experience, splitting alone is inadequate, especially if the residual rectal cuff is longish, because the split may reattach or be retracted/folded as the colon is pulled through and cause rectal stenosis.

The authors' modified L-TAPT using the ARL as the starting point for transanal dissection preserves the innervation of the ATZ, while laparoscopic assistance improves mobilization and maintains the blood supply to the pull-through colon. Despite recent reports of disappointing outcome (including POBF) after TAPT, with or without laparoscopic assistance [8], outcomes should be more reliable if surgeons with a sound knowledge of anatomic relationships in the ATZ commence dissection on the ARL and excise the cuff entirely.

24.7 Other Laparoscopic-Assisted Surgical Procedures

24.7.1 Laparoscopic-Assisted Soave Pull-Through

In 1995, Georgeson et al. reported their primary laparoscopic endorectal pull-through with transanal mucosectomy [1]. Subsequently, their L-TAPT procedure has spread to be performed everywhere, and there are many reports supporting its efficacy [4, 5].

However, some reports indicate that clinical outcomes of pure TAPT and L-TAPT are comparable [12, 13].

L-TAPT has distinct advantages over pure TAPT, such as confirmation of ganglion cells in the proximal bowel segment before transanal dissection intraoperatively and exclusion of torsion and tension related to the pull-through colon before anastomosis (Fig. 24.4). While there are some reports about corrective surgery for torsion of the pull-through colon after pure TAPT and somewhat frequent postoperative internal anal sphincter defects after pure TAPT [14–16], there are no reports indicating that the long-term results of pure TAPT are in any way inferior to those of L-TAPT. In fact, any procedure that allows the surgeon to observe and confirm anatomical relationships more readily must surely have some benefit by eliminating "blind" maneuvers that could otherwise compromise safety.

24.7.2 Laparoscopic-Assisted Swenson Pull-Through

The laparoscopic Swenson pull-through procedure was reported in 1996 [17, 18]. To the best of our knowledge, no case controlled studies have been published using this technique [19]. Overall, postoperative complications and POBF would appear to be more favorable compared with other procedures. In 2011, Hebra et al. reported 12 robotic Swenson pull-throughs, focusing on how effective robot technology was for preventing injuries to the pelvic nerves and vasa deferentia [20]. Further studies are needed to assess long-term outcomes and compare them with the results of other procedures.

24.7.3 Laparoscopic-Assisted Duhamel Pull-Through (L-Duhamel)

In 1994, Smith et al. reported the first successful laparoscopic Duhamel pull-through procedure in a 2-year-old boy [21]. After that, L-Duhamel has become a popular procedure and with numerous reports about its efficacy [22–25], as well as reports comparing the results of L-Duhamel with the open Duhamel procedure. Some reports emphasize that hospital stay is shorter and that oral refeeding is quicker with L-Duhamel [23, 26]. On the other hand, there would appear to be no significant differences between the procedure for postoperative complications and POBF [25, 27]. However, Pierro et al. found there were more rectal spur divisions in L-Duhamel cases than open cases, although the difference was not statistically significant [27]. Nevertheless, they suggested that the L-Duhamel procedure may have a fundamental flaw. Based on this, L-Duhamel should only be performed by skillful surgeons comfortable and confident with the procedure.

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Surgical Management of Total Colonic Aganglionosis and Extensive Aganglionosis

25

Yutaka Kanamori

Total colonic aganglionosis (TCA) is a rare form of Hirschsprung disease and is defined as aganglionosis extending from the rectum to the cecum or distal ileum. Clinically, the length of the distal ileum that is affected by aganglionosis in patients with TCA is defined to be less than 50 cm in Western countries (or less than 30 cm in Japan). The more severe form is called extensive aganglionosis, and the most severe type is called total intestinal aganglionosis in which the entire or nearly entire intestine is affected. TCA and the more severe type of aganglionosis are different from short-segment aganglionosis in several respects as described below, and the management and treatment strategy of TCA and extensive aganglionosis should be considered separately.

The first successful management of TCA was reported in 1953 by Sandegard [1], and since then, many case series have been reported, but the enrolled number of cases was not large because of its rarity. A systematic review with meta-analysis that summarized cases published in the past 30 years was published in 2012 by Laughlin et al. [2], and comprehensive reviews were published in 2012 and 2015 by Moore [3, 4]. These reviews are valuable for obtaining an overall picture of TCA.

25.1 Clinical Characteristics of TCA

TCA is a relatively rare form of aganglionosis, and its incidence has been reported to be approximately 2–13% out of all aganglionosis cases [2, 5]. A recent meta-analysis reported its incidence as 9.1% which was obtained by analyzing published papers from 1980 to 2011 [2].

In contrast to the tendency of male dominance in short-segment aganglionosis, the male-to-female ratio is lower in TCA. The male-to-female ratio was 1.86:1 in a meta-analysis [2], and it was 2.2:1 in a survey of cases over a 5-year period from 1998 to 2002 in Japan [6]. Another important feature of TCA is its high tendency of familial recurrence [3, 4]. The genetic background is not fully understood, but abnormal RET gene signaling and dysregulation of the endothelin system are suspected of being some causes of the abnormal distribution of enteric nerve cells. Some reports showed a higher risk of familial recurrence in longer-segment aganglionosis, and a progression of severity through subsequent generations has been reported [7]. In a nationwide survey of TCA in Japan, the rate of positive family history of TCA was about 11.9% in a recent 5-year period from 1998 to 2002 [6].

In short-segment aganglionosis, the typical first symptom in neonates is intestinal obstructive symptoms such as bilious vomiting and abdominal distention. However, in TCA, some cases do not show typical obstructive symptoms in the neonatal period, and more subtle and milder symptoms appear later in life. Ieiri et al. [6] reported that only 54.5% of TCA patients were diagnosed in the first month of life in Japan. This atypical presentation sometimes makes it difficult to diagnose TCA. Moreover, the radiological and histological characteristics of TCA are different from those of short-segment aganglionosis. Even in neonatal patients with intestinal obstructive symptoms, typical radiological features by contrast enema are not seen. For instance, a typical caliber change between normal and aganglionic bowel is not seen in patients with TCA. In a case series, two TCA patients did not show typical colonic contrast enema findings and were misdiagnosed by radiologists [8]. Another large case series reported that three types of colonic textures were seen by contrast enema among TCA patients [9]: (1) normal caliber (53%), (2) microcolon (29%), and (3) so-called question mark shape (18%). These facts strongly suggest that it is difficult to make a correct diagnosis of TCA from only the results of contrast enema even when we suspect that the patient suffers from TCA, and we should obtain a definitive diagnosis in such cases by the free use of the available diagnostic tools. It is also difficult to make a histological diagnosis of TCA because some cases show faint

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immunohistochemical staining of enteric nerve markers in transition and aganglionic segment and absence of the thick nerve bundle in aganglionic segment [10]. In addition to the atypical pathological findings, the transition zone (in other words, the hypoganglionic segment) may be longer than that in short-segment aganglionosis [3]. If a patient's clinical signs and symptoms suggest TCA, we should be careful when interpreting the pathological findings in biopsy specimens, and it would be necessary to perform repeat biopsies in order to reach a definitive diagnosis when the results are obscure. During the pull-through operation, we should also be careful when distinguishing the sites with normal ganglionic cells and aganglionic sites.

TCA is clinically more severe than short-segment aganglionosis, the overall mortality rate of TCA in a meta-analysis of 969 patients was 19.9% [2], and the postoperative mortality rate after pull-through operation in 739 patients was 5.7% [2]. In a Japanese survey, the mortality rate of TCA was as high as 30.4% about 40 years ago, and it decreased to 7.1% in the recent 5-year period from 1998 to 2002 [6]. It is worth noting that extensive aganglionosis still showed a high mortality rate of 35.5% in the same 5-year period according to the same survey in Japan [6].

Table 25.1 Various operative procedures performed for TCA

1. Martin
2. Duhamel
3. Soave (with or without J pouch)
4. Swenson
5. Colon Patch (Kimura method)
6. Colon patch (Sauer method)
7. TRM-PIAS (transanal rectal mucosectomy and partial internal anal sphincterectomy), proctocolectomy and ileoanal anastomosis
8. Extended myectomy-myotomy of the intestine[a]

TCA total colonic aganglionosis
[a]This procedure is for total or near total intestinal aganglionosis

Table 25.2 Frequencies of various operative procedures performed for TCA

	Laughlin et al. [2]	Ieiri et al. [6]	Blackburn et al. [27]
Martin	31.9%	28.9%	14.3%
Duhamel	31.7%	33.3%	42.9%
Soave	15.7%	15.7%	42.9%
Swenson	5.7%	ND	–
Colon Patch	ND(9.1%)[a]	18.1%	–

TCA total colonic aganglionosis, *ND* not described the rate
[a]The frequency of various operative procedures including colon patch is shown

25.2 Operative Treatment

As described earlier, it is difficult to make an early and exact diagnosis of TCA. It is generally accepted that a definite diagnosis should be made after performing full-thickness biopsy of the intestine and after creating an ileostomy in a normal ganglionic segment by laparotomy. A laparoscopic procedure may replace open laparotomy, and successful one-stage laparoscopic pull-through operation has been reported by some authors [11, 12]. However, the laparoscopic procedure is still not widely accepted, and a long-term follow-up study is needed to determine its feasibility.

Several operative procedures for TCA have been reported (Table 25.1), and the most popular procedure in the past, which was Martin method, was replaced by the Duhamel method (Table 25.2). The Soave method and patch method are also often adopted. Since the first report of the new operative procedure by Martin [13] in 1968, which was a modified technique of the Duhamel operation and where the left side colon is used for water absorption, Martin's technique was the most widely performed technique in the world for several years. A meta-analysis [2] reported that Martin's technique was performed in 230 (31.9%) out of a total of 722 pull-through operations, which had been calculated from cases reported in papers published in the last 30 years. The second most widely performed procedure was the Duhamel method (229/722, 31.7%). The third was the Soave or Swenson method, which is straight ileoanal anastomosis, at a rate of 197/722 (27.3%). Although the Martin method was widely performed in the past, it has become less popular recently due to several reasons. Ieiri et al. [6] reported the frequencies of surgical procedures performed for the treatment of TCA in Japan between 1998 and 2002 as follows: (1) Martin method 28.9%, (2) Duhamel method 33.3%, (3) Soave method 15.7%, and (4) right colon patch method 18.1%. This Japanese survey also reported that the past frequencies of the Martin method were 83.6% in 1978 to 1982 and 53.5% in 1988 to 1992. These rates clearly demonstrate a transition in the preferred surgical technique for TCA by Japanese pediatric surgeons. The reason why the Martin method has been avoided in recent years is that it is a complex procedure with long side-to-side anastomosis. This technique might result in postoperative anastomotic leakage and kinking of the long anastomotic segment, causing periodic obstruction. Also, long anastomosis sometimes causes severe ulcer formation and anemia. Currently, the most popular pull-through method in Japan is the Duhamel method. However, the transanal endorectal pull-through (TAEPT) method with or without laparoscopic assistance has become very popular for the treatment of short-segment aganglionosis, and its rate has become as high as 49.6% during the 5-year period from 2008 to 2012 in Japan [5]. With this tendency, the Soave or Swenson type transanal pull-through method is expected to become the most popular procedure in the future. The right colon patch method was first reported

by Kimura et al. [14] in 1981, and a long-term follow-up study of patients who underwent this procedure showed satisfactory results [15]. With this method, it is expected that water and electrolytes will be absorbed from the right hemicolon, and some pediatric surgeons prefer this method as mentioned above (rate of 18.1% in the 5-year period from 1998 to 2002 in Japan) [6]. However, this procedure is not widely accepted by pediatric surgeons because the surgical procedure is complicated and a staged operation is needed. A similar technique was proposed by Sauer et al. in 1989 [16] in which the ascending colon was used as a patch and the ileocecal valve was preserved. The modified one-stage technique was also reported by the same author in 1993 [17]. Recently, in a long-term follow-up study of patients who underwent this procedure, the patients maintained a good quality of life, although the bowel function score was low in TCA patients treated by this technique [18].

Several modifications of the operative procedure for TCA have been proposed to reduce the postoperative complications. One of the modifications is J-pouch creation in ileoanal anastomosis to preserve the retaining ability of feces in the ileum and to prevent postoperative perineal excoriation [19]. However, pouchitis is an adverse effect. Another modification is to add internal anal sphincterectomy or sphincterotomy in ileoanal anastomosis to prevent postoperative obstruction syndrome and enteritis [20, 21], and its feasibility was reported by Li et al. [22] in 2016.

Creating a covering ileostomy at the time of pull-through operation is one option to prevent postoperative severe perineal excoriation. Bischoff et al. [23] insisted that the covered ileostomy should be kept open until the patient is completely toilet-trained for urine and can sit on a potty. This proposal remains controversial, and some pediatric surgeons do not agree with this because intimate perineal skin care can prevent severe perineal excoriation. In order to reach a definite conclusion concerning this issue, a prospective controlled study should be performed in the future.

Extensive aganglionosis is more difficult to treat than TCA, and a very specific treatment strategy may be needed. Patients with extensive aganglionosis suffer from short bowel syndrome without a colon, and intravenous hyperalimentation is often needed. One novel operation for the treatment of total intestinal aganglionosis was proposed by Ziegler et al. [24] in 1993. The operation is the extended myectomy-myotomy method with jejunostomy created at the 40 cm distal site from Treitz ligament. The authors reported 16 cases treated by this method, and the survival rate was 62.5%, and some patients could tolerate enteral feeding to various degrees. Another operative option for total intestinal aganglionosis is intestinal transplantation or multivisceral transplantation, and a recent meta-analysis by Nakamura et al. [25] showed promising results with an overall survival rate of 66%.

Table 25.3 Complications after pull-through operation for TCA

1. Anastomosis breakdown (leak, abscess, fistula, peritonitis)
2. Enteritis
3. Obstructive syndrome
4. Perineal excoriation
5. Incontinence and soiling

TCA total colonic aganglionosis

25.3 Postoperative Complications (Table 25.3)

As mentioned above, several complications may occur after pull-through operation despite various operative modifications. The most serious problem is postoperative enteritis. According to the meta-analysis, 42% of TCA patients experienced enteritis after pull-through operation [2], and in another report 55.4% of patients experienced enteritis [26]. Enteritis may be triggered by congestion of intestinal fluid and overgrowth of harmful bacteria. However, it has been hypothesized that some immunological defect might exist in the normo-ganglionic segment of the intestine in patients with aganglionosis, thereby causing severe inflammation and enteritis. These issues are still open for discussion and further studies are needed. Postoperative perineal excoriation is another complication. This complication may be prevented by intimate skin care provided by specialists such as wound, ostomy, and continence nurses. However, if refractory soiling and incontinence do exist for some reason, it is very difficult to avoid perineal dermatitis and deep skin injury. In some cases, permanent ileostomy was the final selection to resolve the problem. Bischoff et al. [23] emphasized that a proper and meticulous operative technique is needed to solve this problem. Obstructive syndrome sometimes occurs when the pull-through operation is done using a long aganglionic segment, and this symptom may result in severe ulcer formation and intestinal bleeding. Bischoff et al. proposed a radical opinion that we should abandon all complex techniques such as the patch procedure and J-pouch formation to prevent this complication [23].

25.4 Does an Optimal Operative Procedure for the Treatment of TCA Exist or Not?

The optimal operative technique for TCA is still uncertain even though several controlled studies have been performed in the past [26–29]. Such studies were not prospective controlled studies, and the number of patients enrolled was small. We do not have a definitive conclusion for the question of which operative technique is optimal for TCA. This is also supported by the fact that the postoperative complication rates are very similar among several different techniques. The rate of postoperative enteritis is still high after any surgi-

cal technique with any added option, and we must develop a new treatment strategy to prevent enteritis and to preserve and activate residual bowel function at the maximum level. It is strongly expected that a completely novel idea to reconstruct a normally nerved ileum and colon will be developed by adopting a stem cell technology or some other promising strategy.

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Complications

26

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26.1 Introduction

Since Swenson reported the definitive surgical procedure for Hirschsprung's disease (HD) which removes the whole aganglionic segment and pulls the more proximal normoganglionic bowel down to the anal canal, various kinds of procedures have been devised to lessen intra- and postoperative risks and complications. Generally, full-thickness rectal dissection (Swenson), endorectal dissection (Soave), and retrorectal pull-through (Duhamel) have ever been considered as the basic surgical procedures for HD repair. Besides, laparoscope-assisted (LAPT) and trans-anal pull-through (TAPT) procedures have emerged as smaller incision or less invasive approaches replacing laparotomy for the above definitive operations, and they have nearly become standard in recent years. Although the three basic procedures and their recent modifications have achieved similar and excellent results in most patients with HD, there remain several early and late postoperative complications; especially, the latter is unique and more important to HD patients and includes persistent obstruction or constipation, recurrent HD-associated enterocolitis (HAEC), and incontinence.

Recent reviews of long-term outcome after TAPT revealed that 14.2% of the patients had persistent symptoms postoperatively (constipation in 53.3% of those patients, incontinence/soiling in 17.8%, and enterocolitis in 28.9%). Redo surgery was required in 3% [1]. Regarding LAPT, nearly a third of the patients continue to have long-term bowel problems [2]. There have been controversies over differences in impacts of initial definitive surgical procedures on short-, intermediate-, and long-term outcomes as well as complications. Some studies demonstrated that postoperative bowel functions and complications varied widely depending on the different surgical procedures, however, others found no significant difference [3–5].

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There have been unsolved problems in analyzing postoperative bowel functions and complications in patients with HD. Firstly, consensus on definition of each complication and evaluation standards for bowel functions are lacking. Secondly, timing to make the above assessment has not been standardized. Because postoperative fecal control, though impaired during childhood, improves significantly with age, the incidence of enterocolitis, constipation, and incontinence declines significantly with time [6, 7]. Therefore, prospective studies with unified methods are vital when the postsurgical outcome is to be compared between different definitive surgical repairs for HD or between institutions.

26.2 Early Postoperative Complications

Colorectal surgery is a key to complete repair for HD, and it may be associated with early postoperative complications such as wound infection, bleeding, anastomotic leak, and abscess. Although those complications are not unique for HD, when serious enough, they may influence life-long colorectal functions and result in impairment of quality of life.

26.2.1 Infection

In general, colorectal surgery has been associated with the highest risk of surgical site infection (SSI) and other infectious complications. In historical reviews of HD, the incidence of wound infection was reported to range from 1.7% to 19.2% [8, 9]. More recent analysis of surgical site infection (SSI) in pediatric colorectal surgery has revealed that the incidence of total SSI, which includes superficial/deep incisional infection (incisional SSI) plus organ/space infection (OSI), is 5.3% in patients with HD (incisional SSI 3.1%, OSI 2.2%). By surgical procedure the total SSI rate is around 2% for partial colectomy with or without ostomy and 5% for pull-through with or without ostomy [10].

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26.2.2 Leak

Anastomotic leak is a rare but devastating complication causing anastomotic stricture, pelvic abscess, Soave cuff abscess, and sepsis, which may require diverting stoma and redo operation (Fig. 26.1). Risk factors of leak include impaired blood supply of the pull-through bowel, high tension at the anastomosis, failure in managing caliber discrepancy, rectal dissection in the wrong plane, pelvic contamination, wound healing problems such as preoperative malnutrition or steroid treatment, and early postoperative rectal manipulation. Historical studies showed that the rate of leak ranged from 0 to 16.1%, stricture from 0 to 42%, and abscess formation in 2–6% of the HD patients [8, 11–13]. Recent reviews have reported extremely lower leak rate of 0%, 3%, and 2.1% for trans-anal Soave, Swenson, and Duhamel procedure, respectively, without significant difference between surgical procedures, probably thanks to refinement of operative procedures and pre- and postoperative management [14, 15].

26.3 Late Complications

26.3.1 Enterocolitis

Hirschsprung-associated enterocolitis (HAEC) is an inflammatory disorder potentially leading to serious morbidity and mortality in HD patients and occurring not only prior to but also following definitive repairs. Reported incidences of HAEC range from 6 to 50% before surgery, while its incidence after surgery also varies from 2 to 35% [16]. Postoperative HAEC may occur any time after definitive surgery, mostly within a few years of the surgery [17]. Although the cause of postoperative HAEC is unknown, basic and clinical research has proposed various theories of its pathogenesis including fecal stasis due to mechanical obstruction (retained aganglionic colon, transition zone pull-through, stricture, sphincter achalasia, tight muscular cuff, etc.), alteration of mucin component or prostaglandin activity in the mucosa, *Clostridium difficile* or rotavirus infection, impaired mucosal immune system, and genetic factors [18, 19].

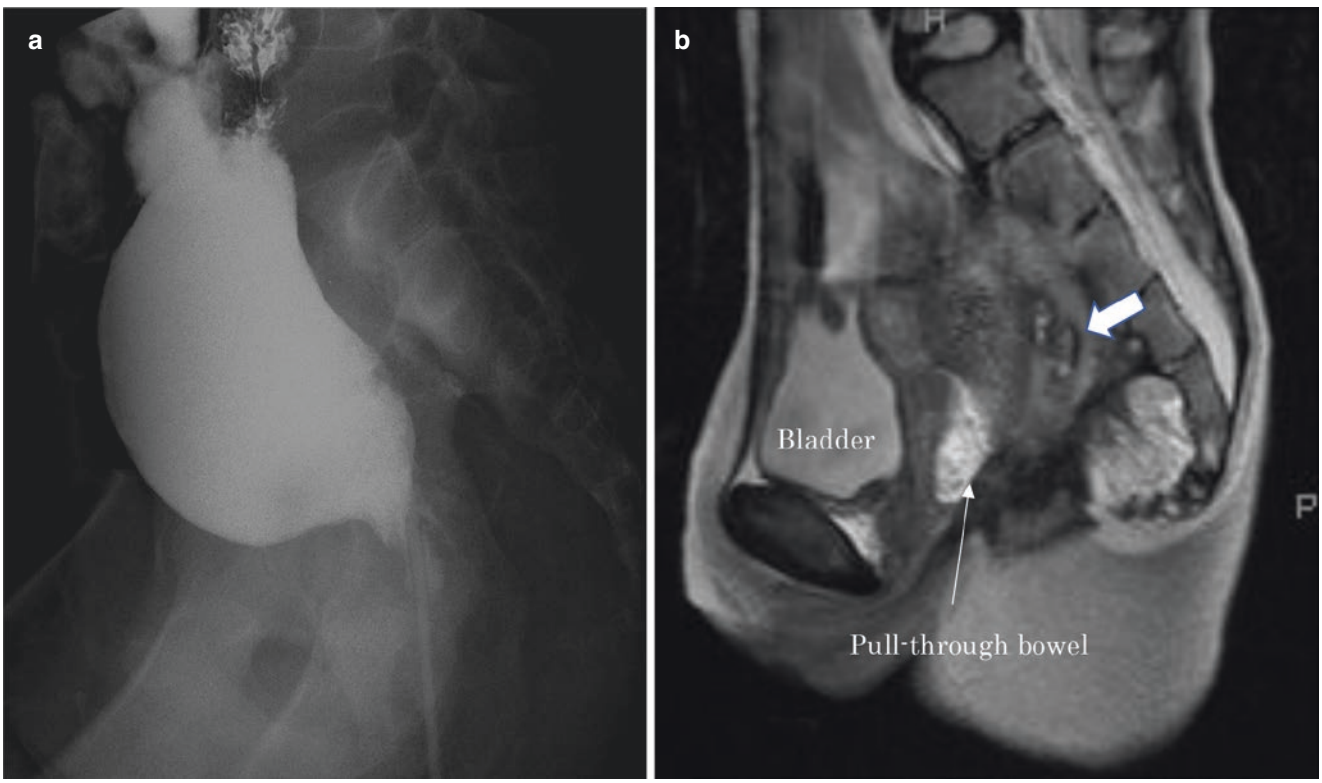

Fig. 26.1 Intractable anorectal stricture following repeated anastomotic insufficiency. (**a**) Gastrografin enema showing anorectal stricture, (**b**) MRI showing infectious granulation tissue in the presacral area behind the pull-through bowel

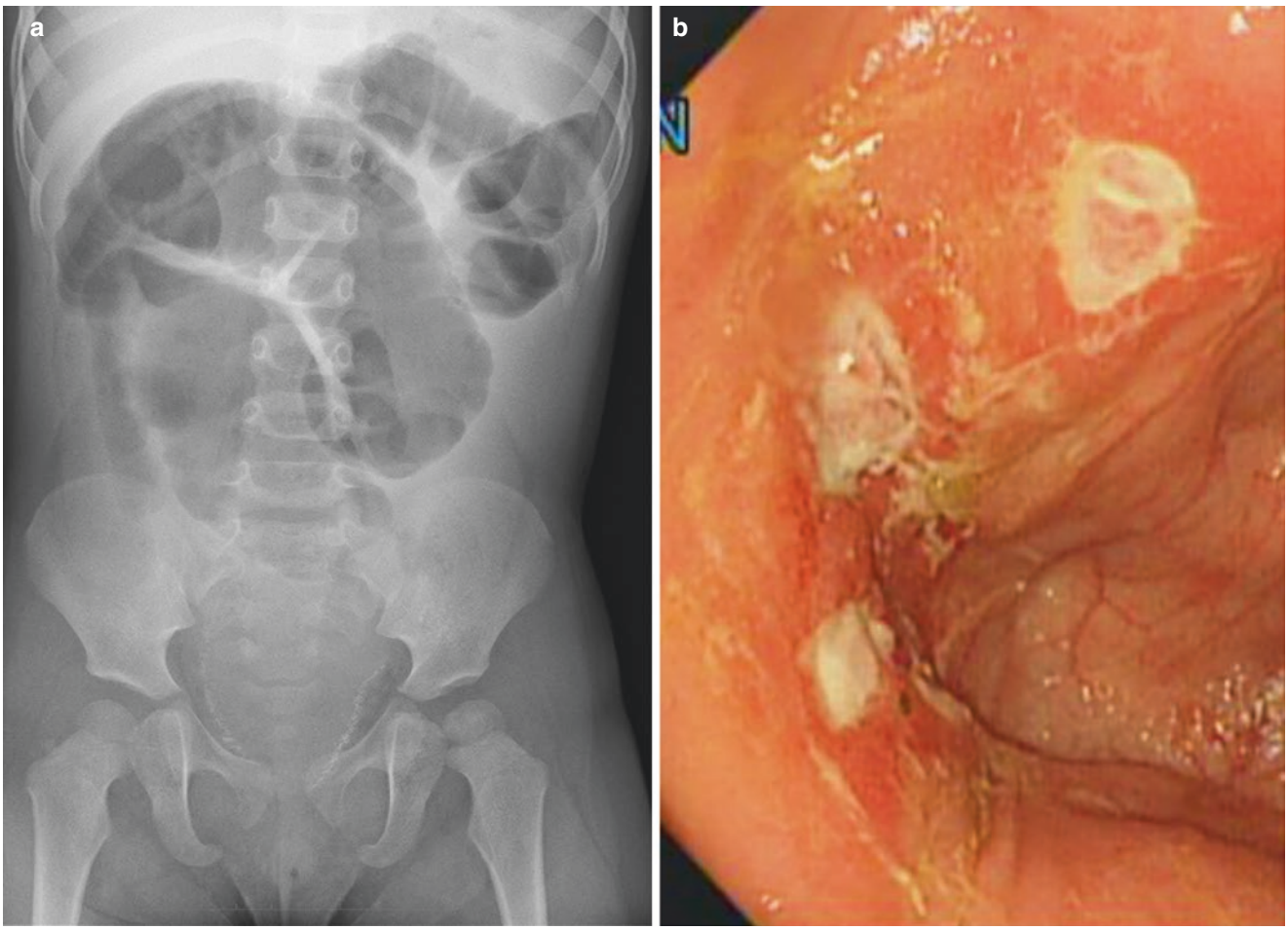

Fig. 26.2 Enterocolitis. (**a**) X-ray showing bowel distention after trans-anal Soave procedure, (**b**) Endoscopic view of multiple rectal ulcers after Duhamel procedure

26.3.1.1 Symptoms and Signs

Clinical manifestations of HAEC include abdominal distention, explosive diarrhea, vomiting, fever, lethargy, and rectal bleeding, which are nonspecific for HAEC, hindering early definitive diagnosis (Fig. 26.2). However, considering high mortality around 30% associated with HAEC even after surgery [20, 21], early diagnosis and prompt treatment are mandatory to avoid delay in diagnosis and disease progression.

26.3.1.2 Diagnosis

To establish a common basis for the diagnosis of HAEC, a HAEC scoring system has been developed by expert pediatric gastroenterologists and surgeons participating in a Delphi process [22]. The score is calculated by summing up 16 items regarding a clinical history and physical, radiologic, and laboratory findings. A score of 10 or greater is considered as HAEC. However, this scoring system has not been considered useful for clinical decision-making because of lacking clinical validation [23]. Recently, another guideline for the diagnosis and management of HAEC has been proposed in the United States. It is based on the clinical grade system described by the Michigan group, which resembled the staging system established by Bell for necrotizing enterocolitis [24, 25] (Fig. 26.3). It grades HAEC from grade I (possible HAEC) through grade III (severe HAEC) based on clinical history, physical examination, and radiological findings.

26.3.1.3 Risk Factors

Several risk factors of HAEC have been reported so far, which may explain its pathophysiology. Preoperative history of enterocolitis, younger age at diagnosis and repair, and long-segment type of HD have been considered higher risk of HAEC [26], though the latter has become controversial in recent literature [27]. Trisomy 21 has generally been viewed as a strong risk factor of HAEC, and about half of trisomy 21 patients with HD have developed HAEC [28, 29]. Regarding each definitive repair, the incidence of HAEC has ranged from 1% to 39% for Duhamel operation, 6% to 23% for Soave operation, and 25% to 28% for Swenson and Boley procedures, and there are controversies about the correlation

Grade	Description	Clinical History	Physical Examination	Radiographic Findings
I	Possible HAEC	❑ Anorexia ❑ Diarrhea	❑ Mild abdominal distention	❑ Normal ❑ Mild ileus gas pattern
II	Definite HAEC	❑ History of past episode of HAEC ❑ Explosive diarrhea ❑ Fevers ❑ Lethargy	❑ Fever ❑ Tachycardia ❑ Abdominal distention ❑ Abdominal tenderness ❑ Explosive gas/stool on DRE	❑ Ileus gas pattern ❑ Air/fluid levels ❑ Dilated loops of bowel ❑ Recto-sigmoid cutoff
III	Severe HAEC	❑ Obstipation ❑ Obtunded	❑ Decreased peripheral perfusion ❑ Hypotension ❑ Altered mentation ❑ Marked abdominal distention ❑ Peritonitis	❑ Pneumatosis ❑ Pneumoperitoneum

Fig. 26.3 Guideline for the diagnosis of HAEC. Guideline for the diagnosis and grading of HAEC from grade I (possible HAEC) through grade III (severe HAEC) based on clinical history, physical examination, and radiographic findings (*HAEC* Hirschsprung-associated enterocolitis, *DRE* digital rectal examination). (Gosain A, Frykman PK, Cowles RA, et al. Guidelines for the diagnosis and management of Hirschsprung-associated enterocolitis. Pediatr Surg Int 2017, 33(5): 517–521)

between the incidence of HAEC and the types of definitive repair [9, 27, 30, 31]. According to recent study, up to 54% of patients experienced at least 1 episode of enterocolitis after TAPT, and 21% experienced >4 episodes; however, there was an age-related decline in the incidence of HAEC [7]. Another important postoperative risk factor of HAEC is persistent bowel obstruction caused by retained aganglionic segment, transition zone pull-through, anastomotic stricture, twisted bowel pull-through, tight muscular cuff following the Soave procedure, and dysmotility of the ganglionic intestine. Supporting those findings, the Pittsburgh series revealed that the patients with anal canal damaged during the TAPT developed fecal incontinence and no postoperative enterocolitis after surgery [32].

26.3.1.4 Management

As mentioned above, early recognition and diagnosis are mandatory for the right treatment at the right time. In cases with definite HAEC, bowel rest by prohibiting oral intake except small amount of clear fluids and intravenous fluid resuscitation with or without nasogastric tube decompression should be started first according to the above guideline [25]. Rectal decompression and irrigation are recommended in the absence of peritonitis or necrosis to resolve intestinal fluid stasis as well as to check fecal properties and bacterial survey. Oral or parenteral administration of metronidazole and broad-spectrum intravenous antibiotics including either ampicillin and gentamicin combination, piperacillin/tazobactam, or aztreonam should be considered when systemic infection suspected [25, 33] (Fig. 26.4). In cases of severe HAEC without response to nonsurgical treatment described before, laparotomy followed by resection of a necrotic segment, proximal bowel diversion, and intraperitoneal drainage may be indicated in an intensive care setting.

26.3.1.5 Prevention

There have been several proposals to prevent postoperative HAEC. Routine rectal irrigation with 10–20 mL/kg aliquots 1–2 times daily for 3–6 months has decreased incidence and severity of HAEC after operative repair [34]. Prophylactic antibiotic therapy to prevent recurrent episodes of HAEC is controversial because of increased risk of selecting resistant organism. However, metronidazole is generally recommended for prompt therapy to prevent aggravation of early-stage HAEC [33]. Therapy with probiotics, which are live microbes playing a protective role in intestinal mucosal integrity and promoting mucin production, has been found to decrease the incidence and severity of postoperative HAEC in a recent study. However, it remains to be controversial [35].

26.3.1.6 Recurrence

Patients with recurrent episodes of HAEC after definitive surgeries should be checked for anatomic and pathologic causes including anastomotic stricture, obstructing Soave cuff, kink or twist of pull-through bowels, enlarged post-Duhamel pouch, and retained aganglionic segment [33]. Therefore, physical examination, contrast enema, and rectal biopsy (suction or full thickness) are recommended to rule

Grade	Description	Diet	Antibiotics	Irrigations	Surgery
I	Outpatient	❑ Oral hydration	❑ PO metronidazole	❑ Consider rectal irrigations	
II	Outpatient or inpatient	❑ Clear liquids or NPO ❑ IVF hydration	❑ Metronidazole (PO or IV) ❑ Consider broad spectrum coverage [ampicillin (IV) and gentarmicin (IV) or pipercillin/tarobactam(IV)]	❑ Rectal irrigations	
III	Inpatient, possible ICU	❑ NPO ❑ IVF hydration	❑ PO metronidarole ❑ Broad spectrum coverage [ampicillin (IV) and gentamicin (IV) or piperacillin/tazobactam (IV)]	❑ Rectal irrigations	❑ Proximal diversion for failure to improve with non-operative management ❑ Exploration for pneumoperitoneum

Fig. 26.4 Guideline for the management of HAEC. Guideline for the management of HAEC based on grade. Considerations for diet, antibiotics, rectal irrigations, and need for surgery are listed by grade (*PO* per os, *NPO* nothing per os, *ICU* intensive care unit, *IV* intravenous, *IVF* intravenous fluid). (Gosain A, Frykman PK, Cowles RA, et al. Guidelines for the diagnosis and management of Hirschsprung-associated enterocolitis. Pediatr Surg Int 2017, 33(5): 517–521)

out the above causes. Although transition zone (TZ) pull-through has also been regarded as a cause of obstruction, retained TZ is not easy to define after surgery, and there are a lot of controversies about relations between TZ pull-through and impaired bowel passage [36].

What is an appropriate treatment of recurrent HAEC depends on its anatomic or pathologic causes. A trial of dilatation is a first choice for anastomotic strictures and obstructing Soave cuff. When the trial is unsuccessful or there remains another anatomic etiology such as a twisted pull-through, retained aganglionic segment, or TZ pull-through, various kinds of redo pull-through approaches have been recommended including a redo Soave [37], Swenson [5], and a Duhamel approach [38]. The approaches may also be chosen on a case-by-case basis in consideration of the previous failed procedures, level of anastomosis, impaired rectal blood supply, perirectal inflammation, and fibrosis [39]. Although some reports have suggested that the outcome of redo surgery is similar with that of primary pull-through surgery, the redo should be avoided as much as possible because it tends to be associated with postoperative morbidities including incontinence and cosmetic issues.

When there is no anatomic or pathologic culprit for HAEC, so-called internal sphincter achalasia (ISA) may be a possible cause of postoperative rectal stasis and obstruction leading to HAEC. Treatment options for ISA include intrasphincteric botulinum toxin (Botox®) injection or internal sphincter myotomy/myectomy. The former is relatively a new agent expected to reduce the tonus of internal sphincter muscle without damaging it. The Botox has been reported effective to reduce the incidence of HAEC and safe enough for injection repetition [40, 41]. However, its effect differs from one case to the next and is difficult to predict [42]. On the other hand, myectomy has been done for more than 30 years for patients with postoperative obstruction in HD [43]. More than 70% of them after myectomy have been reported to respond well with colitis relieved. However, soiling after myectomy may occur in 20–25% of the patients [44, 45].

26.3.2 Constipation

Constipation is one of the major long-term complications following HD repair surgery with the incidence ranging from 6 to 34%, which is minimized when the patients are in the age of adolescence [46]. Historically, higher rates of constipation were reported in Swenson procedure [47] or Duhamel procedure [48], while subsequent studies revealed no statistically significant differences in bowel function between those procedures [49]. A more recent study of bowel functions after TAPT has shown the incidence of constipation (5%) similar with that in the age- and gender-matched controls (4%) and much lower than in historical series after the Duhamel, Soave, and Swenson procedures [7]. Its associations with surgical procedures have been controversial because interinstitutional comparison of bowel function and complications is very difficult due to lack of common standards of definitions of bowel functions and complications.

26.3.2.1 Etiology

Constipation can be attributed largely to similar factors inducing bowel obstruction and HAEC which were mentioned above. Strictures can develop not only at the site of anastomosis due to technical failure or anastomotic insufficiency but also at the Soave muscular cuff narrowing due to its surrounding fibrosis or rolling down of the cuff itself [50] (Fig. 26.5). To avoid these complications, especially those

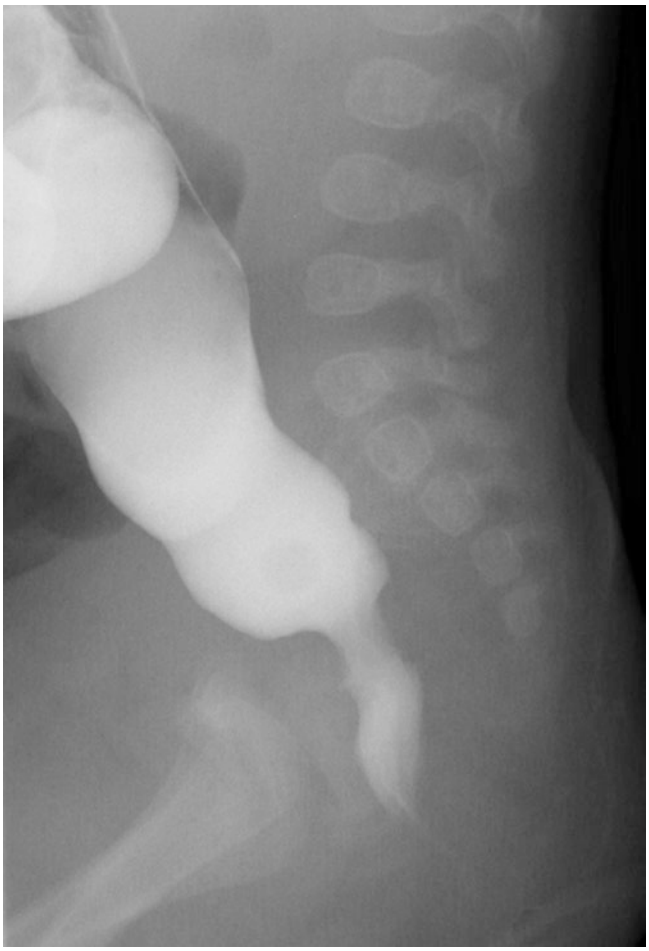

Fig. 26.5 Presumed postoperative Soave cuff stenosis. Ba enema showing anorectal stenosis after trans-anal Soave procedure, which ameliorated after conservative therapy (bougie, rectal irrigation)

associated with Soave procedure, some studies recommend leaving a short cuff with the muscle only 1–2 cm above the dentate line or leaving no cuff by switching to trans-anal Swenson procedure [15, 51]. Twisting of the pull-through bowel is another cause of bowel obstruction and constipation, which is likely to require surgical revision. Diverticular enlargement of the aganglionic pouch after the Duhamel procedure is also reported to cause fecaloma and obstruct the pull-through bowel. Ikeda's Z-shaped anastomosis using the GIA instrument is an excellent procedure to prevent this problem by completing side-to-side anastomosis between the aganglionic rectum and the ganglionic pull-through bowel without remaining rectal pouch [52]. Remaining aganglionic segment or TZ pull-through is also considered as a culprit of constipation. TZ pull-through has been reported to increase a risk of enterocolitis to 61% and require revision surgery in 28% [53]. However, there are controversies about the definition of TZ pull-through [36], which hinders comparative studies. Firstly, there are various discrepancies between radiological and pathological TZ [54]. Secondly, its pathological diagnosis itself is tricky and sometimes inaccurate because submucosal and intramuscular ganglion cells are distributed unevenly in a circumferential direction of the bowel wall [55, 56]. Although much rare, secondary aganglionosis has been reported to develop several months or years following pull-through procedures and cause abdominal distention, pain, constipation, and soiling. Its etiology may include ischemia, infection, or abnormal innervation, but the details have been unknown [57, 58].

While HD repair surgery aims at eliminating the aganglionic segment and TZ, it has been supposed that physiological dysfunction is not always limited to the aganglionic segment but also affects other areas of the bowel. Although not routine diagnostic test, motility studies may be suggestive in this respect. Pittsburg group classified colonic motility disorders after HD repair into four patterns: (#1) strong colonic contractions propagating through the neorectum, (#2) functional fecal retention (stool holding) with normal colonic contraction, (#3) ineffective colonic contraction due to neuropathy (supposedly, intestinal neuronal dysplasia), and (#4) hypertensive internal anal sphincter with normal colonic contraction (internal anal achalasia) [59]. In other studies, the pattern #2 of the motility disorder has been named as "functional megacolon caused by stool-holding behavior" or "dyssynergic defecation" [60]. Different managements for the constipation have been proposed on the basis of the motility patterns, for example, a bowel management including laxatives, enemas, high-fiber diet, and biofeedback therapy for the pattern #2, or partial resection of the bowel for focal lesions with pattern #3. In some severe cases of obstructive symptoms, antegrade enema through cecostomy or temporary proximal stoma to decompress the colon is another option [61].

26.3.2.2 Diagnosis

Various methods have been applied to look for potential causes of constipations. A digital rectal exam and a contrast enema will clearly demonstrate dilatation, stricture, kinking, twisting of the bowel, or a narrow muscular Soave cuff. Full-thickness biopsy of the pull-through bowel is required to demonstrate the presence of remaining or acquired aganglionosis, TZ, or so-called intestinal neuronal dysplasia. Some researchers have analyzed patterns of colonic motility after HD repair using colonic manometry and proposed appropriate interventions according to the patterns as mentioned above [59, 62]. Motility analyses can also be performed by radiopaque marker transit study or nuclear medicine colonic transit study [63, 64]. Following thorough assessment of constipations, transabdominal ultrasound of the rectum may be useful for further evaluation of the bowel management during the follow-up [65].

26.3.2.3 Management

Appropriate treatment for constipation depends on its cause and pathophysiology. Mechanical obstruction due to anastomotic stricture or cuff narrowing after Soave procedure is an indication of serial sessions of dilatation with various success rates. In a 10- to 12-month-old infant, the anorectum has eventually been dilated up to a #14 Hegar [66]. Revision surgery will be the next option when dilatation is ineffective or when the pull-through colon is twisting or kinking. In the absence of mechanical obstruction, repeat rectal biopsy and pathological review of the proximal resection margin in the first pull-through are required to check for neuromuscular abnormalities in the pull-through bowel. The patients with retaining aganglionosis, TZ pull-through, or dilatation-irresponsive narrow Soave cuff often require further surgical intervention including myectomy/myotomy [45, 67] or redo pull-through [50]. On the other hand, functional constipation without mechanical and pathological abnormalities after HD repair is reported to subside with time after early childhood to the incidence of around 10% [46], and likewise, most cases of internal sphincter achalasia may spontaneously resolve over time (around age 5 years or later) [68]. Therefore, nonoperative approaches should be considered first to avoid surgical interventions with potential for incontinence. Representative examples of nonoperative approaches are botulinum toxin [40, 69], aggressive bowel management, and biofeedback training [60]. In any case, treatment for constipation after HD repair should be chosen on an individual basis based on the symptoms, initial surgeries, imaging, and laboratory findings.

26.3.3 Incontinence

Poor fecal control, especially incontinence, is a crucial postoperative complication which has a great negative impact on quality of life, hampering social lives in older children. The incidence of incontinence after HD repair has ranged between 7% and 75%, varying a lot depending on its definition and assessment [31, 49, 70–73].

26.3.3.1 Etiology

Except for overflow incontinence due to constipation, the causes of incontinence after HD repair remain controversial and have been pursued in various studies. At present, two distinct underlying mechanisms have been speculated for the causes of incontinence: first, abnormal colonic hypermotility and, second, surgical impairment of anal sphincters and nerves.

Evidence of the former mechanism is that high-amplitude propagated contractions (HAPCs) reaching the neorectum (pull-through bowel) have been found increased enough to raise the luminal pressures above the anal sphincter contractions in children with postoperative fecal soiling [59]. To support this finding, radionuclide scanning has also demonstrated rapid transit in the proximal, ganglionated colon in HD children with fecal soiling [74]. Recently, a part of this rapid transit has been suspected as potentially adverse reactions to food [75].

Regarding the latter mechanism, it has been assumed that postoperative fecal control is more or less influenced by technical features of various repair surgeries including Soave, Duhamel, and Swenson procedures, which are further subdivided into transabdominal or trans-anal (TAPT) approaches in recent years. El-Sawaf et al. compared fecal control between transabdominal and trans-anal Soave procedures. Although no significant difference in the fecal control was found between them, the continence score was twice better in the transabdominal approach compared with that in the trans-anal approach [76]. Goseman et al. also showed a poorer fecal control in patients who underwent trans-anal approach compared with those who underwent transabdominal approaches [77]. Another study revealed greater impairment in quality of life, especially continence, in patients who underwent trans-anal Soave procedure compared with those who underwent transabdominal Duhamel procedure [3].

The levels of anastomosis of a pull-through bowel have been considered very important for fecal control regardless whether transabdominal or trans-anal approach is adopted. In contrast to the anastomosis at the rectum, the anastomosis at the skin, anoderm, pectinate line, or a combination of those can cause damage to the anal canal and result in fecal incontinence and no enterocolitis [32, 78]. However, what length of the aganglionic rectum should be retained below the anastomosis is controversial. Swenson's original level of anastomosis is 2 cm posteriorly and 3 cm anteriorly from the pectinate line in more than 1-year-old patients [79]. While the length between 0.5 and 1 cm above the dentate line is a classical standard for transabdominal Soave, 2 cm above the dentate line or anorectal line has recently been proposed as a new level of the anastomosis for trans-anal Soave procedure [32, 80]. Apart from the anastomotic levels, overstretching of the anus during trans-anal Soave procedure may also cause long-term external sphincter damage leading to soiling or incontinence [81]. However, on the other hand, a long-term follow-up study of trans-anal Soave procedures has revealed that fecal control including soiling or incontinence may improve significantly with age and finally the patients can achieve social continence in adulthood [7].

26.3.3.2 Diagnosis

In order to manage incontinence properly, it is very important to differentiate true soiling from pseudoincontinence secondary to fecal impaction. In the case of true incontinence, inspection of the site of the anastomosis of the pull-through bowel is mandatory to clarify whether the anal

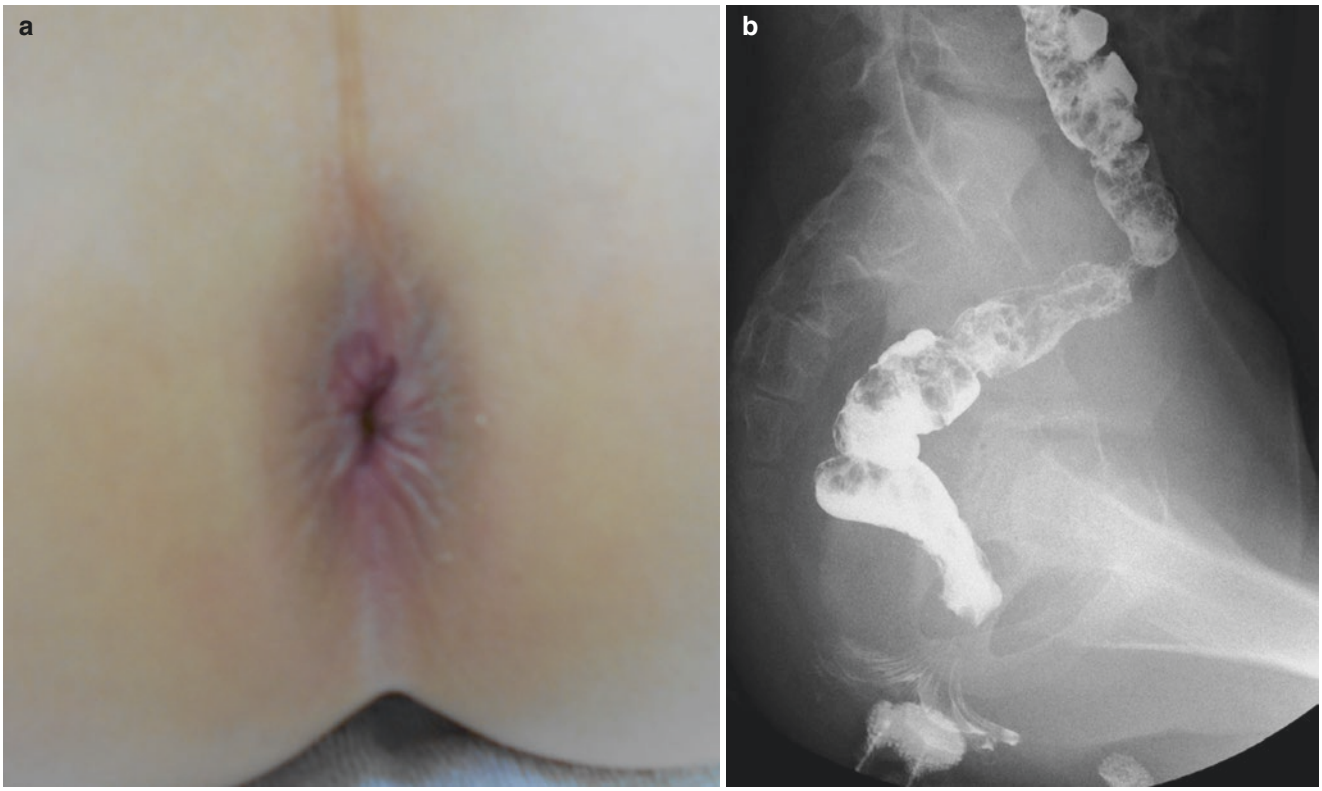

Fig. 26.6 Incontinence after trans-anal endorectal pull-through operation. (**a**) Patulous anus, (**b**) Hypotonic anal sphincter

canal is preserved or not. The anus with sphincter compromise looks lax or flaccid, and it is described as "patulous anus" [78] (Fig. 26.6). Barium enema will show the length and diameter of the colon as well as the presence or absence of stricture or fecal impaction. When anatomical abnormalities are ruled out, bowel motility studies including manometry [62] or colonic transit study mentioned in the previous section may be useful to analyze anal resting pressures and rectal peristalsis. Hydrogen breath tests may provide an important clue to the diagnosis of poor carbohydrate digestion and absorption in the case of incontinence with diarrhea [75].

26.3.3.3 Management

Conservative nonoperative management should be a first choice for patients with incontinence because a lot of studies have reported that continence is improved with age [82]. However, it may not be improved until late adolescence and insufficient continence may have a long-term catastrophic impact on their quality of life. Therefore, incontinence should not be left untreated but scrutinized carefully to pursuit its causes. As pointed out by Bischoff et al., the most important issue is whether anorectal function including anal sensation or anal sphincter is damaged or not. When pseudoincontinence excluded, they have recommended loperamide, constipating diet, bulking agents (water-soluble fiber), and limited number of meals during the day for the patients with a preserved anal canal mucosa and sphincter [78]. This regimen shares similarity with another study's recommendation which aims at reducing the amplitude and frequency of HAPCs by anticholinergics and loperamide (0.4–1.0 mg/kg/day) for patients with hyperperistalsis through the neorectum after HD repair [59]. In patients with incontinence due to sugar malabsorption, exclusion diet of FODMAP sugars (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) and loperamide may be effective to improve fecal consistency and continence [75]. More intractable is the incontinence due to intraoperative damage to the anal canal from inappropriate mucosal dissection and/or from overstretching of the anal sphincters. That damage can lead to deterioration of anal sensation and sphincter tonus, which has generally been considered irreversible and unrepairable by redo surgery [83]. Therefore, a daily large volume saline-based enema including antegrade enemas or construction of the permanent stoma has been recommended as the last option left for those patients [84]. Recently, Kanazawa group in Japan reported the effectiveness of anal canal plasty by folding of the posterior wall of the anal canal in those patients with "patulous anus" which was, presumably, caused by overstretching of the anal sphincters or over-splitting of the posterior Soave cuff during the primary operation [85]. Although short-term outcome of

the operation seems promising, whether its effect lasts in the long-term has remained unknown.

26.3.4 IBD-Like Lesions

Inflammatory bowel diseases (IBD) are chronic inflammatory gastrointestinal diseases of unknown etiology, and although rare, their association with HD has been gradually accumulated in the literature [86]. Because they have similar clinical symptoms with HAEC such as diarrhea, hematochezia, and abdominal pain, further investigation including biopsies may be required to definitely diagnose postoperative HD patients with IBD. According to the recent review of the literature, mean age at diagnosis of IBD was 7.7 years, the majority (73%) of patients were male, 86% of patients had either total colonic aganglionosis or long-segment aganglionosis, and 84% of the patients had undergone a Duhamel pull-through procedure [87]. Most of the patients with HD and IBD had Crohn's disease (72.3%). Although rare, IBD associated with HD should be considered during the long-term follow-up when patients with HD develop enterocolitis after surgery.

26.3.5 Voiding and Sexual Dysfunction

Because of pelvic manipulation during any pull-through procedures, there is a risk of intraoperative damage to urinary tract or intrapelvic autonomic nerves (hypogastric plexus and pelvic splanchnic nerves), which may cause urinary dysfunction. Various modifications of pull-through procedures including endorectal pull-through and Duhamel's procedure are designed to avoid such intraoperative damage. However, there have been only a few studies analyzing urinary and sexual functions after the pull-through procedures. Most recent review of the literature has reported around 1% incidence of intraoperative injuries to the urethra, ureter, or vagina, respectively, and 2% incidence of urinary incontinence and a few percent of other urological symptoms [88]. No statistical difference in urinary incontinence or voiding functions was found between postoperative patients (mostly after the Soave procedure) and controls [89]. However, as constipation and urologic problems have close relationship with each other in general (not limited to patients with HD), bowel as well as voiding assessment and their management are important for better quality of life.

Sexual dysfunction after surgery is also difficult to assess and requires long-term follow-up. The literature analyzing marital lives of the patients with HD decades ago reported sexual dysfunction in 1% of the patients after the Soave, 9% after the Duhamel, and 10% after the Swenson [26]. However, sexual outcome has not been assessed actively or systematically in the recent literature, causing lack of evidence to understand relationship between sexual outcome and surgical procedures [88].

26.4 Mortality

Although the incidence of mortality varies depending on the eras of treatment and length of follow-up, the recent data have shown that it is around 3% with the range from 2% to 13.4% [11, 12, 21, 90]. Down's syndrome, HAEC, length of aganglionosis, and associated anomalies (especially congenital heart disease) have been reported as possible risk factors for mortality. Although occurring less frequently in these days than in the historical past, HAEC has remained to be a potentially life-threatening complication unique to HD before as well as after the definitive surgery. As described in the guideline, prevention of HAEC occurrence, its early recognition, diagnosis, and right treatment at the right time are very important to reduce mortality due to HAEC [25].

26.5 Conclusion

Various options for a definitive HD repair are available now that LAPT and TAPT procedures have recently been well received and replacing classical laparotomy approaches. Although the majority of the patients achieve a satisfactory or excellent outcome after those minimally invasive approaches, early and late complications remain an important issue affecting the long-term outcome and quality of life of the patients. Some of those complications may be related closely to the surgical techniques employed in the definitive operation in addition to nonsurgical intrinsic factors. Therefore, further refinement and appropriate indication of surgical procedure need to be established. Close and long-term follow-up based on intra- or interinstitutionally shared standard of assessment and surgical procedures is mandatory to precisely analyze and overcome those complications.

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Long-Term Results, General

27

Hiroomi Okuyama

27.1 Introduction

The outcomes of Hirschsprung disease (HD) have improved significantly because of significant developments in the understanding of the pathologic anatomy and physiology. Therefore, measurement of functional outcomes and quality of life are having an increasingly important role, especially in pediatric patients with operated HD.

Many factors influence on the outcomes of HD, including length of aganglionic segment, types of operative procedure, and approaches. In addition, HD has been reported to be associated with additional congenital anomalies or syndromes in approximately 20–30% of infants. All these factors are closely related to the survival rate and the long-term outcomes of HD. Therefore, in order to describe the long-term results of HD in general, it is necessary to separate these factors.

Although there is no standard definition of long-term outcome, in order to reliably evaluate defecation habit, such as incontinence and constipation, at least 3 years' follow-up is necessary. In this section, the literature which reported more than 3 years' follow-up have been mainly reviewed with respect to the following indices: survival rate, bowel function, physical and mental development, genitourinary function, and QoL.

27.2 Survival

27.2.1 Overall Survival

The prognosis of patients with non-syndromatic HD in whom the aganglionic segment is within the colon is fairly good in terms of survival. In contrast, patients with syndromatic HD or with extensive aganglionosis carry higher risk for long-term mortality and morbidity. Patients with universal aganglionosis have extremely poor long-term survival unless the patients receive small bowel transplantation.

A report of 260 patients treated for HD in a single US center in1992 showed that the overall survival rate was 93.8% (244/260). An increased mortality was associated with Down syndrome, total colonic aganglionosis, and enterocolitis [1].

More recent reports showed that the overall survival rate of patients with HD has been improved.

A retrospective nationwide survey of HD in Japan for four decades (Group 1, between 1978 and 1982; Group 2, between 1988 and 1992; Group 3, between 1998 and 2002; and Group 4, between 2008 and 2012) showed that the mortality rate decreased over time from 6.5% in Group 1 to 2.4% in Group 4 [2].

Another nationwide, population-based cohort study in Swedish patients with HD between 1964 and 2013 showed that the mortality rate in the HD cohort was 3%, which was higher than in controls also when data were adjusted for Down syndrome. The cohort median aged 19 years (2–49) included 739 individuals with HD and 7390 controls. 3.0% HD died at median age 2.5 years compared to 0.7% controls at median age 20 years. The Kaplan–Meier analysis showed significantly lower survival rate in the HD cohort (Fig. 27.1) [3].

These nationwide studies showed that the overall survival rate of patients with HD has been improved up to 97% but still remains lower compared to control.

27.2.2 Total Colon Aganglionosis (TCA) Including Extensive and Universal Aganglionosis

TCA is one of the most significant factors related to the long-term mortality and morbidity of HD. The previous reports revealed that the overall survival rate of patients

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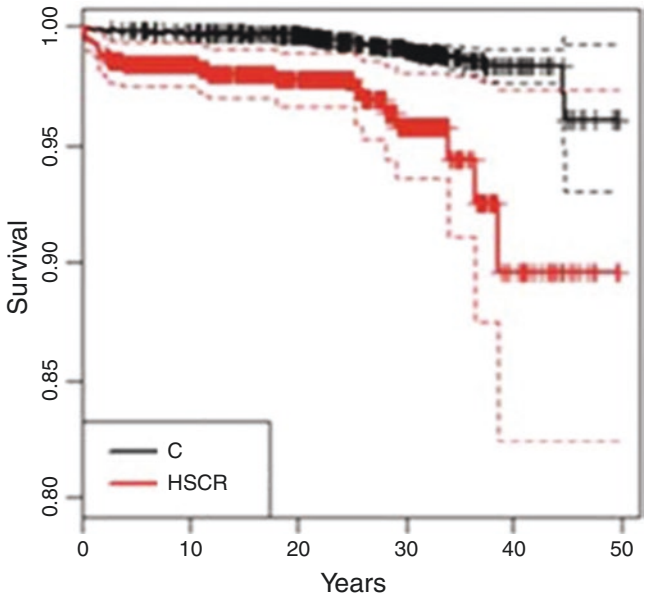

Fig. 27.1 Kaplan–Meier analysis for total survival for the HD cohort and controls [3]

with TCA were 94% (45/48) [4], 80% (29/36) [5], and 97% (56/58) [6].

Among these reports, compared to distal ileum group, patients with aganglionosis extending to mid small bowel had a significantly poorer survival rate.

The survival rates of patients with extensive aganglionosis have also improved recently as those of patients in whom the aganglionic segment is within the colon. A retrospective nationwide survey of HD in Japan for four decades (Group 1, between 1978 and 1982; Group 2, between 1988 and 1992; Group 3, between 1998 and 2002; and Group 4, between 2008 and 2012) showed that there has been remarkable improvement in the mortality rate associated with the small intestine (aganglionosis extending orally to more than 30 cm of the terminal ileum). The rates were 53.6% in Group 1, 33.3% in Group 2, 35.5% in Group 3, and 25.5% in Group 4 [2].

Aganglionosis involving most of the small bowel has a highest morbidity and mortality rate. Although the number of cases was limited, long-term survival rate ranged from 28% (2/7) [7] to 40% (2/5) [8]. Most of them died of severe enteritis, liver dysfunction, and TPN complications. These patients are thought to be candidates for small bowel transplantation.

27.3 Bowel Function

Some earlier studies on patients with operated HD reported excellent bowel function. Normal bowel habit was found in more than 90% of 195 patients followed for at least 15 years after Swenson operation [8]. Good to excellent anal function was reported in 2430 patients followed for 15–30 years after Duhamel operation [9]. In contrast, more recent studies based on detailed questionnaire and interview have revealed much higher incidence of long-term bowel dysfunction, affecting between 30% and 80% of patients [10]. The ratio of patients with completely normal bowel function was much lower than that surgeons expected. In addition, it has become apparent that the functional defects in children with HD are passed on to adulthood in a significant proportion of patients. Recent prospective and adequately controlled studies reveal that constipation and fecal soiling are common late sequelae in adulthood and that HD patients show uniformly lower scores of overall bowel function than healthy control subjects [11]. Because incontinence and soiling impair the quality of life, the functional results of surgical therapy remain unsatisfactory.

The long-term results of HD vary based on the methodology by which functional outcome was assessed in these patients. Therefore, in this section, several assessment tools of bowel function were described, and then the long-term functional results and the influence of aging and TCA on the long-term bowel function were described.

27.3.1 Assessment of Bowel Function

Historically, there are several assessment systems of bowel function in patients with anorectal anomalies and HD. Anorectal function has been objectively measured by the Kelly scoring system [12], the modified Wingspread score [13], and the Holschneider scoring system [14]. These scoring systems, consisting of both subjective and objective measurement, classify the functional outcomes into three to four grades.

Recently, several new scoring systems for pediatric patients based on more detailed questionnaire and interview have been proposed. Rintala et al. proposed a bowel function scoring (BFS) system to assess fecal soiling and constipation in patients with anorectal anomalies [15, 16]. The BFS is a multivariate scoring method by seven items with a maximum score of 20 (Table 27.1). A BFS $\geq$ 17 was taken as the lower limit of a good/normal functional outcome. It has been previously validated for the evaluation of bowel function in patients with anorectal malformations, and some data from controls are available [17]. Fichtner-Feigl et al. proposed another pediatric incontinence and constipation scoring system (PICSS) [18]. A simple-to-apply questionnaire-based scoring system for the diagnosis of incontinence, constipation, and combinations of the two was specially developed for use in children (Table 27.2). These measurement tools are easy to score, can be completed by either the child or their parents, and do not require

Table 27.1 Bowel function score (BFS) [15, 16]

Evaluation on feel continence	Score
Feels the urge to defecate	
Always	3
Most of the time	2
Uncertain	1
Absent	0
Ability to hold back defecation	
Always	3
Problems less than once a week	2
Weekly problems	1
No voluntary control	0
Frequency of defecation	
Every other day—twice a day	3
More often	2
Less often	1
Soiling	
Never	3
Staining less than once a week, no charge of underwear required	2
Frequent staining/soiling, charge of underwear required	1
Daily soiling, requires protective aids	0
Accidents	
Never	3
Less than once a week	2
Weekly accidents, often requires protective aids	1
Daily, protective aids required day and night	0
Constipation	
No constipation	3
Manageable with diet	2
Manageable with laxatives	1
Manageable with enemas	0
Social problems	
No social problems	3
Sometimes (foul odors)	2
Problems causing restrictions in social life	1
Major social/psychosocial problems	0

a physical examination. In addition to these scoring systems, many unique evaluation methods are also used in different studies.

27.3.2 Literature Review of Long-Term Outcomes of Bowel Function

An earlier study on long-term outcomes of patients aged 9.9 (0.5–36) years showed that surgical reconstruction for HD provides near normal gastrointestinal function for the majority of children, but long-term follow-up shows significant residual problem with soiling in 12.6% of the patients [19]. Since this study did not use standardized evaluation system for bowel function, the result could not be compared to the recent outcomes assessed by the detailed scoring systems. A recent study using the evacuation score (max 8, min 0) on the long-term outcome of their 146 patients median aged

Table 27.2 A pediatric incontinence and constipation scoring system (PICSS) [18]

Pediatric incontinence/constipation score	Incontinence	Constipation
Does your child wear diapers during the day?		
Always	0	–
Sometimes	2.5	–
No	5	–
Does your child wear diapers during the night?		
Always	0	–
Sometimes	2.5	–
No	5	–
How often does your child open its bowels?		
Several times a day	0	4
Once daily	2.5	2
Less often	5	0
What does the stool usually look like?		
Watery	0	1
Variable	2	0.5
Thick	4	0
Can your child control the urge to open its bowels?		
Yes always	5	–
Sometimes	2.5	–
No	0	–
Can your child tell the difference between stool and air in the bowels?		
Yes always	4	1
Sometimes	2	0.5
No	0	0
Does your child regularly soil its underclothes by involuntarily passing small amounts of stools?		
Yes always	–	0
Sometimes	–	1
No	–	2
Does your child have trouble opening its bowels completely (incomplete emptying)?		
Yes always	–	0
Sometimes	–	1.5
No	–	3
Does your child feel pain when opening its bowels?		
Yes always	2	0
Sometimes	1	2
No	0	4
Does your child have press hard to empty its bowels?		
Yes	2	0
Normal	1	2
No	0	4
Does your child have a lot of wind?		
Yes always	–	0
Sometimes	–	1
Never	–	2
Does your child suffer from constipation?		
Yes always	–	0
Sometimes	–	2
Never	–	4
Does your child have pains in the tummy?		
Yes always	–	0
Sometimes	–	2
Never	–	4
Total score		

33 years (19–55) showed that the evacuation score was rated as "excellent (7–8)" in 66.7%, "good (5–6)" in 19.0%, "fair (3–4)" in 11.9%, and "poor (0–2)" in 2.4%. Therefore, 85.7% were considered to have a satisfactory bowel function. However, only 21.4% had a completely normal score of 8/8. Incontinence occurred in 16.7%, and soiling was present in 19.0% of the questionnaire respondents [20]. Another recent study by the bowel disease questionnaire to 48 adult patients aged 28 (20–43) years in Sweden showed that the bowel function was impaired in the HD group compared to controls, especially problems with flatulence, the need to strain at defecation, and several defecations for emptying. Patients in the HD group also had significantly more problems with fecal incontinence than controls [21]. The most recent study using the BFS systems on long-term outcomes of 146 patients with HD between 1986 and 2011 showed that, compared with controls, patients reported impairment of all aspects of fecal control except constipation and that 75% of patients were socially continent. Soiling, fecal accidents, rectal sensation, and ability to withhold defecation improved with age to levels comparable to controls by adulthood, but stooling frequency remained higher in 44% of patients. Compared with matched controls, significant impairment of fecal control prevails after transanal endorectal pull-through in HD patients during childhood, but symptoms diminish with age [11].

There is a systematic review on long-term bowel function of HD operated with transanal endorectal pull-through. Six studies with 316 patients (at least 3 years follow-up) were included in the analysis (Table 27.3). Most patients had a daily defecation frequency of one to three bowel movements 3 years postoperatively, similar to the healthy controls. They concluded that 15% of all patients operated with transanal endorectal pull-through continue to experience persistent bowel symptoms with constipation as the main problem [22].

According to the literature review of long-term outcomes of HD patients, earlier studies tended to underestimate the real incidence of bowel dysfunction. Careful assessment by objective scoring systems is necessary during adolescence and adulthood to reliably estimate the long-term bowel function in patients with operated HD.

27.3.3 Comparisons Between Different Surgical Procedures

Historically, several established surgical procedures including Soave, Swenson, and Duhamel procedure have been applied for HD. However, there have been no randomized controlled trials to compare these surgical procedures or approaches. Most of the comparative studies of long-term outcomes between different procedures are retrospective based on the limited number of cases.

Natalie et al. reported that long-term functional outcomes of 69 adult patients were not significantly different among the types of pull-through, aside from more constipation associated with the Duhamel procedure [29]. El-Sawaf et al. reported that the long-term study showed significantly better (twofold) results regarding the continence score for the abdominal approach compared with the transanal pull-through. The stool pattern and enterocolitis scores were somewhat better for the transanal endorectal pull-through group [30]. In contrast to this study, a multicenter comparison study of long-term results of patients with transanal vs transabdominal approach showed that transanal endorectal pull-through was associated with fewer complications and fewer episodes of enterocolitis. Transanal endorectal pull-through patients did not have a higher rate of incontinence. They conclude that use of transanal endorectal pull-through was an excellent surgical approach for children with HD [31]. A main limitation of these retrospective studies was the small number of cases and the large number of patients lost to follow-up. To date, there is no conclusion as to which method is superior to others. However, because of the less invasiveness of the procedures, laparoscopic and transanal approaches have become standard procedures in recent years.

Table 27.3 Characteristic long-term outcome of included TAPT studies [22]

Study (author, year)	No. of patients	Follow-up time (average, years)	Total no. of patients with bowel problems	Specific problems in bowel function			Secondary surgery, no.
				Constipation	Incontinence	Enterocolitis	
Dutta (2010) [23]	20	3.00	7	4	1	2	
Graneli et al. (2015) [24]	24	4.00	11	8		3	3
Khalil (2015) [25]	53	5.80	9	4	5		
Kim and Oh (2009) [26]	61	3.20	6	1	1	4	4
Kohno et al. (2007) [27]	21	4.83	6	4		2	
Yang et al. (2012) [28]	137	4.67	6	3	1	2	3
Total	316	4.30	45 (14.2%)	24 (53.3%)	8 (17.8%)	13 (28.9%)	10 (3.2%)

27.3.4 The Influence of Aging on Bowel Function

The influence of aging on bowel function in patients with HD remains unclear.

Jarvi et al. reported that bowel function evaluated with the BFS system deteriorates with increasing age after operated HD [10]. As this study included exclusively adult patients (92 patients, mean age 43 years), the results can apply only to adulthood. In contrast to this report, Natalie et al. found that most children significantly improve with respect to fecal continence, based on the long-term follow-up data of 69 adult patients [29]. Another study by questionnaire to 51 patients aged 3–21 years showed that fecal continence improved significantly with age and was the strongest predictor of QOL scores of all variables in the study [32]. A prospective follow-up study of the outcome of transanal endorectal pull-through (31 patients, endorectal one-stage pull-through) showed that an initial high frequency of daily stools, median 12 stools/day, reaching an acceptable situation with median 4 stools/day after 1 year. After 4 years, the number of stools did not differ significantly from healthy controls [33]. A study using the PICSS on 51 consecutive children showed that improved continence should be expected with time, but constipation often continues to be an ongoing problem [34]. The most recent study showed that soiling, fecal accidents, rectal sensation, and ability to withhold defecation improved with age to levels comparable to controls by adulthood, but stooling frequency remained higher in 44% of patients [11].

A major limitation of these retrospective studies was the limited number of patients, and a significant portion of patients was lost to follow-up. Therefore, the effect of aging in the functional outcome remains unclear. However, most of the recent studies using objective assessment tools during childhood showed that bowel function improves with age onto adulthood.

27.3.5 TCA, Extensive

There have been few reports on the long-term outcome of bowel function of TCA and extensive aganglionosis, and most of those are small series with various types of operation.

Tsuji et al. [4] reviewed their experience in the management of 48 patients with TCA over a 17-year period. Permanent stoma was necessary in six patients. The average number of bowel movements decreased annually as did the incidence of fecal incontinence. There was no difference between the various procedures in the long-term follow-up. Nighttime incontinence appears to be one of the major long-term problems after the Martin procedure. Anorectal function improves gradually with age. Menezes et al. [6] reviewed the long-term (2–31 years) outcome in 58 patients with TCA. Three patients had opted for permanent ileostomies because of intractable incontinence or recurrent enterocolitis. Of the 42 patients in whom bowel function was assessed, 22 had normal bowel control, and 20 were soiling. At 5 years, patients had an average of 5.2 bowel movements per day, which reduced to a mean of 3.4 per day at the age of 15 years. There was a nationwide survey of 27 patients with TCA in Sweden 1995–2014 [35]. The median follow-up time was 9.5 years. All 17 patients aged >4 years old completed the BFS questionnaire at median age of 10 (4–20) years. Median stool frequency/day was 5 (1–30). Fecal accidents at least once per week were reported by four (24%), and social problems by eight (47%). The median BFS was 15 (11–19) without any gender differences. One-third of patients with TCA report obstructive symptoms, one-third need additional nutrition, and one-fifth require a permanent stoma.

As bowel dysfunction is more frequent in patients with TCA than in patients with common types of HD, TCA has a negative impact on long-term bowel function. However, according to these recent reports, bowel function of patients with TCA improves with age.

27.4 Physical and Mental Development

27.4.1 Overall

There are several factors that are thought to worsen the long-term physical and mental development in patients with HD.

Long-segment aganglionosis extending up to small bowel can cause physical growth retardation due to malabsorption. In addition, some sort of central nervous system anomalies, which are closely related to the enteric nervous system maldevelopment, may put infants with HD at higher risk of developmental delay. Surgery and general anesthesia in the neonatal period may also contribute to neurodevelopmental delay. Despite these factors that could exert adverse effects on the long-term outcomes, overall physical and mental development of HD patients has been reported to be satisfactory.

Moore et al., in a follow-up study of 178 children more than 4 years old with HD, found that the overall growth was within normal limits. They also found that younger children were more likely to be underweight but that growth tended to improve with age. Satisfactory school performance was achieved in 74% [36]. More et al. reported that at 1 year of age, many infants with HD have

ongoing gastrointestinal problems. Their overall growth appears satisfactory, and most infants are developing normally based on a retrospective study of 44 infants with HD (40 with short and 11 with long segment and 3 with TCA) [37].

In contrast to these good long-term results of HD, there is a certain proportion of disturbed physical growth in patients with TCA. Tsuji et al. found that 25% of 5 year olds with TCA were at <2nd percentile for weight at 5 years rising to 63% at 15 years [4]. Weight z-scores were normal or near normal and did not differ among TCA subgroups, whereas height z-scores were significantly lower among those with proximal small bowel compared to distal ileal involvement [38]. A nationwide survey of 27 patients with TCA in Sweden 1995–2014 (median follow-up time 9.5 years) showed that 8 patients required parenteral support, until a median age of 11 (2–24) months. Oral energy support was used by 5/27 (15%); still 5/22 (23%) were underweighted [35]. According to these previous reports, most infants with HD develop normally. However, growth retardation appeared to be common in patients with TCA. Long-term follow-up of physical and mental development is necessary especially for this higher-risk group of HD.

27.5 Genitourinary Function

There is limited information available on genitourinary function in patients with HD in the long-term follow-up period.

Ieiri et al. reported that the genitourinary function was considered to be within the reference range, and urinary problems were minimal using a questionnaire survey of 43 patients aged 19–55 years [20]. An assessment study by questionnaire to 48 adult patients aged 28 (20–43) years shows no difference in urinary function between HD and control. In the HD group, 3 of 38 had problems with urinary incontinence compared to 5 of 39 controls. Three of 38 patients in the HD group had difficulties empting the urinary bladder, compared to 1 of 39 in the control group [21]. Neuvonen et al. evaluated the lower urinary tract symptoms (LUTS) and sexual function in patients aged >4 years (n = 123) who underwent endorectal pull-through. They found that no significant differences were demonstrated in the overall prevalence of LUTS between patients (67%) and controls (80%). Regarding sexual function, male patients reported sexual satisfaction and erectile function similar to controls. They conclude that endorectal pull-through is safe with regard to preservation of the integrity and functioning of the genitourinary tract [11]. Although the available data were limited, all of the data showed that genitourinary function was considered to be within the normal range and did not influence the social life of these patients. The concept of the classical operative procedures, avoiding potential injury to the pelvic nerve, might account for this good long-term genitourinary function.

27.6 Quality of Life

Recently, measurement of quality of life is having an increasingly important role in pediatric surgical practice as a valuable outcome measure. However, since long-term follow-up is necessary to evaluate the QoL especially in the pediatric population, available data are limited. Recently, several questionnaire-based assessment tools have been used in patients with HD. Different tools are used for different age groups as the following:

1. SF-36 health survey (≥18 years) [39].
2. Gastrointestinal Quality of Life Index (GIQLI) (≥18 years) [40].
3. Pediatric Quality of Life (PedsQL) (4–18 years) [41].
4. PedsQL 4.0 Generic Core Scales (global QoL) [42].

The SF-36 health survey and GIQLI are instruments for measuring QoL for adults, which are easy to use and fulfills stringent criteria of reliability and validity. On the contrary, the PedsQL and PedsQL 4.0 are modular instruments for measuring health-related quality of life in children and adolescents ages 2–18.

An assessment study using PedsQL4.0 questionnaires on 51 patients aged 3–21 years showed that fecal continence was the strongest predictor of QoL scores of all variables. There was no statistically significant difference in QoL scores between children with HD and healthy children, either overall or by age group [32]. Ieiri et al. reported the long-term outcome of 42 patients (median age 33 years), which showed that 45.2% were married, and 68.4% of those married had children. The educational and professional careers of the respondents were successful. They concluded that most patients appeared to be well-adjusted members of society [20]. Another assessment study by questionnaire to 48 adult patients aged 28 (20–43) years showed impaired bowel function and gastrointestinal quality of life in adults treated for HD during childhood. However, the generic quality of life instrument SF-36 could not show any differences between cases and controls [43]. Khalil evaluated health-related quality of life (HRQoL) for children 5–7 years after transanal pull-through operation of HD by using PedsQL and PedsQL4.0. The study concluded that the operation showed a good postoperative long-term HRQoL. Overflow incontinence and age at time of surgery had a significant negative effect on all the aspects of HRQoL [25]. A nationwide, population-based cohort study on all patients with HD, registered in the Swedish National Patient Register, showed that the

highest educational level and the individual disposable income did not differ between patients with HD and controls, indicating that the disease had a low impact on these parameters [21].

According to these recent studies using the validated assessment tools, most of the HD patients appear to be able to function as normal members of the society in terms of psychosocial, occupational, and recreational activities.

27.7 Summary

Overall survival of HD has improved and has reached to satisfactory results. However, there is a risk of impaired bowel function for a long time after surgery, and an impaired bowel function has an adverse influence on quality of life in patients with HD. Many of the long-term problems that these patients experience are specific to HD. The follow-up of HD patients should be performed by medical personnel familiar with the disease, preferably in a specialized referral center, and the follow-up program.

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Long-Term Result of Ikeda Z-Shaped Anastomosis

28

Satoshi Ieiri and Tomoaki Taguchi

28.1 Introduction

Hirschsprung's disease has been one of the main target disorders in pediatric surgeons for long time. A variety of procedures have been developed to perform a definitive operation for Hirschsprung's disease including three standard procedures: the Swenson procedure [1], the Duhamel procedure [2], and the Soave procedure [3].

Ikeda K devised modified Duhamel procedure "Ikeda-Z procedure" in 1963 to eliminate the rectal pouch and to achieve complete resection of the septum between the aganglionic rectum and the normal colon. The procedure was published in 1967 [4]. Briefly, after the suturing of the posterior wall of the rectum and the pulled-down colon is completed on the dentate line from the anal side, a transverse incision is made on the anterior wall of the colon at the level of the peritoneal reflection from the abdominal approach. A specially designed oval-shaped crushing clamp is applied to perform complete resection of the colorectal septum. Then the upper end of the anterior wall of the rectum and the incised anterior wall of the normal colon is anastomosed in interrupted sutures. In other words, an end-to-end anastomosis is performed halfway around horizontally at two places, the upper and lower parts. After introduction of linear stapler instead of the crushing clamp, the operative procedure and postoperative management of such patients have become easier. Recently, laparoscopic approach of Ikeda-Z procedure was performed [5].

Four nationwide surveys in Japan revealed Z-shaped anastomosis to be one of the representative operative procedures [6–8]. Definitive operative procedures have been established for Hirschsprung's disease, and there is almost no operative mortality, except for total colonic aganglionosis with small bowel involvement [8].

Pediatric surgeons have to take care regarding not only the anorectal functions but also the genitourinary functions and the social performance in the postoperative state. In particular, the bowel function and quality of life including the social performance should be elucidated in Hirschsprung's disease patients who have undergone a definitive operation and reached adolescence. The aim of this chapter is to present the long-term postoperative outcome of the general condition, bowel function, and social performance of those who had Hirschsprung's disease in childhood and who had undergone definitive operations mostly Ikeda-Z procedure at the single institution [9, 10].

28.2 Long-Term Bowel Functional Outcome of Ikeda-Z Procedure

From 1963 to 1997, 127 patients with Hirschsprung's disease underwent Z-shaped anastomosis at Kyushu University Hospital, and 122 of 127 patients (96%) survived. The present status and symptoms of the surviving patients, including their social circumstances and physical development, were evaluated. This study was based on personal interviews using a standardized format developed by two of the authors. The same questionnaire was sent by mail to the patients who now lived at distant locations. Anthropomorphic evaluation for weight and height was based on the standard deviations of each age group, according to the annual reports of the Japanese Ministry of Health and Welfare and the Ministry of Education. Status of evacuation was evaluated based on the following symptoms: diarrhea, constipation, incontinence, and soiling. Scoring was 2 points for none, 1 point for sometimes, and 0 points for always. A total of 7–8 points was estimated to be excellent, 5–6 points was good, 3–4 points was fair, and 0–2 was poor. Anorectal function tests, including manometric study and barium enema, were regularly

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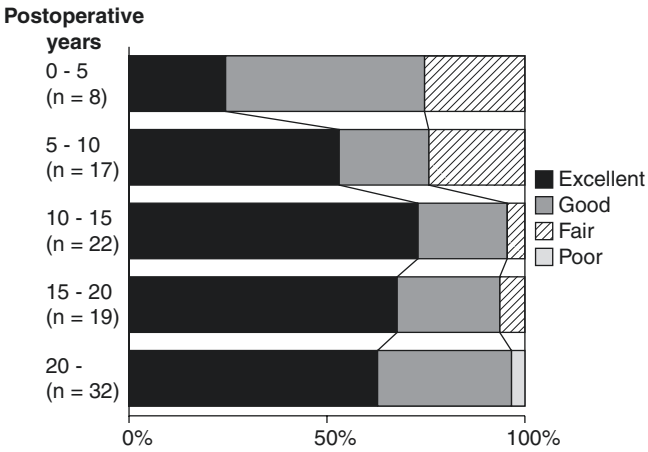

Fig. 28.1 Evacuation score. Cited from "Fig. 2" of Suita S, Taguchi T, Yanai K, Kamimura T, Nakao M, Ikeda K: Long-term outcomes and quality of life after Z-shaped anastomosis for Hirschsprung's disease. J Am Coll Surg. 1998 Dec;187(6):577–83

performed during clinical follow-up. Manometric studies were done 432 times in 86 patients, and barium enema studies were done 226 times in 80 patients. The parameters of manometric study were the mean resting pressures of the anal canal and of the rectum (normal control, between 20 and 40 cm H_2O in the anal canal and between 5 and 10 cm H_2O in the rectum, in children) and the positive rates of the presence of the anal canal rhythmic contractions and the recto-sphincteric reflex (normal control, 100% of control children show positive in both parameters) (Fig. 28.1). For barium enema studies, there were four parameters: (1) megarectum (the criteria of megarectum are based on a ratio of the maximal rectal diameter and the distance between both sides of the ischial spines of more than 75% on frontal X-ray view); (2) recto-anal angulation (presence of the sharp angle of rectal floor line against pubococcygeal line on lateral X-ray view; normal control shows the sharp angle); (3) anal canal staining (positive visualization of anal canal after removal of the rectal tube; normal control shows negative staining); and (4) leakage (leakage of contrast medium after removal of the rectal tube; normal control shows no leakage). Statistical analysis was performed using unpaired *t*-test and Fisher's exact probability. Probability values of less than 0.05 were considered statistically significant.

28.2.1 General Status

Current status of body weight was available for 106 out of 122 patients (87%), and height was available for 99 patients (81%). Regarding body weight, 74 patients (70%) were within ±1 SD, 17 (16%) were between −1 SD and −2 SD, 3 (3%) were less than −2 SD, and 12 (11%) were more than 1 SD. In height, 71 patients (71%) were within ±1 SD, 14 (14%) were between −1 SD and −2 SD, 5 (5%) were less than −2 SD, and 9 (9%) were more than 1 SD.

28.2.2 Status of Evacuation

As a result, 99 out of 122 patients (81%) could be fully evaluated for this study, and the mean postoperative period was 17 years. The evacuation scores for all patients were as follows: excellent, 62.2%; good, 28.6%; fair, 8.2%; and poor, 1.0%. The percentage of the patients who showed severe symptoms was 4.1% for diarrhea, 3.1% for constipation, 5.1% for incontinence, and 7.1% for soiling. Regarding age, 79 out of 96 patients had already survived more than 12 years (high school age or more) since undergoing operation (mean postoperative period 23 years). The evacuation scores of this age group were excellent, 65.8%; good, 26.6%; fair, 6.3%; and poor, 1.3%. Patients in this age group with severe symptoms were 3.8% for diarrhea, 1.3% for constipation, 2.5% for incontinence, and 3.8% for soiling. The incidence of incontinence and soiling markedly decreased in high school age patients. The evacuation score increased chronologically and reached a plateau 10–15 years after operation (Fig. 28.1). The sense of defecation also appeared chronologically (Fig. 28.2). Only 45% of the patients had a sense of defecation within 5 years after operation; 82% had it after 10 years and 100% after 15 years. Defecation scores were also compared with type of operation. There was no significant difference in scores between the primary operation and secondary operation, but the scores of the patients after reoperation

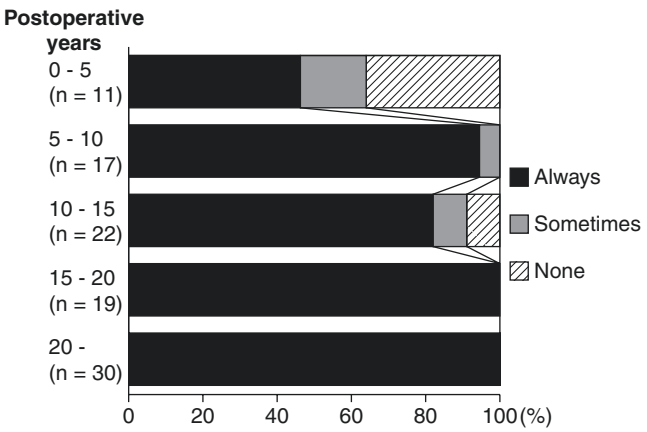

Fig. 28.2 Sense of defecation. Cited from "Fig. 3" of Suita S, Taguchi T, Yanai K, Kamimura T, Nakao M, Ikeda K: Long-term outcomes and quality of life after Z-shaped anastomosis for Hirschsprung's disease. J Am Coll Surg. 1998 Dec;187(6):577–83

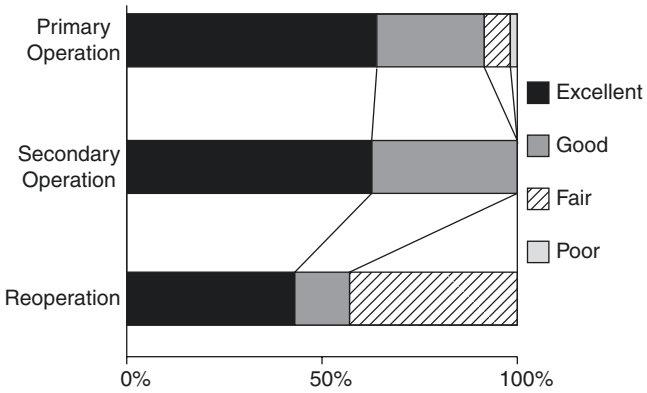

Fig. 28.3 Evacuation score based on type of defection. Cited from "Fig. 4" of Suita S, Taguchi T, Yanai K, Kamimura T, Nakao M, Ikeda K: Long-term outcomes and quality of life after Z-shaped anastomosis for Hirschsprung's disease. J Am Coll Surg. 1998 Dec;187(6):577–83

were lower than those of patients after primary and secondary operation (Fig. 28.3).

28.2.3 Manometric Study

Manometric studies were done 432 times in 86 patients. The mean resting pressure of the anal canal was 33.5 cm H_2O, and that of the rectum was 7.3 cm H_2O. The positive rate of the anal canal rhythmic contractions and the rectosphincteric reflex, including the atypical one, were 86.3% and 40.5%, respectively. The postoperative chronologic change in the mean resting pressure of the anal canal and of the rectum is shown in Fig. 28.4. The pressure difference between the anal canal and the rectum increased over time. The postoperative chronologic changes in the positive rate of anal canal rhythmic contractions and the rectosphincteric reflex are also shown in Fig. 28.5. About 80% of the patients constantly showed positive anal canal rhythmic contractions. The positive rate of the reflex at first tended to increase over time and thereafter decreased. The relationship between the symptoms and manometric findings is shown in Table 28.1. Patients with incontinence showed significantly high rectal resting pressures, and the patients with soiling showed significantly low positive rates for rectosphincteric reflex. Patients with constipation showed high anal canal resting pressures, but there was no statistical significance. The relationship between the evacuation score and the positive rate of the rectosphincteric reflex is shown in Table 28.2. The patients with better function showed a positive rectosphincteric reflex, but only 18% of the "excellent" cases showed a positive reflex, and 54% of the "good" cases showed a positive reflex.

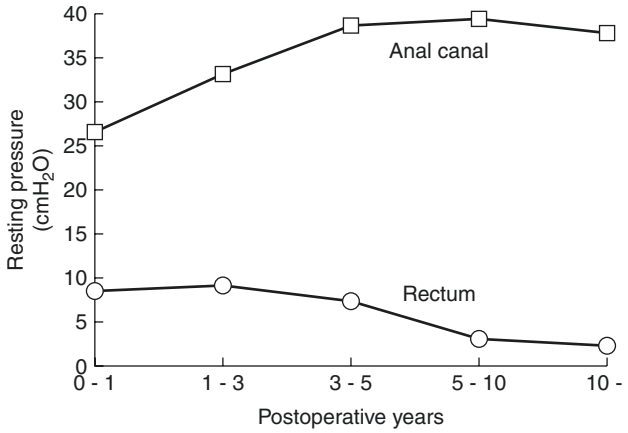

Fig. 28.4 Chronologic changes in the postoperative anal canal and rectal resting pressures based on a manometric study. Cited from "Fig. 5" of Suita S, Taguchi T, Yanai K, Kamimura T, Nakao M, Ikeda K: Long-term outcomes and quality of life after Z-shaped anastomosis for Hirschsprung's disease. J Am Coll Surg. 1998 Dec;187(6):577–83

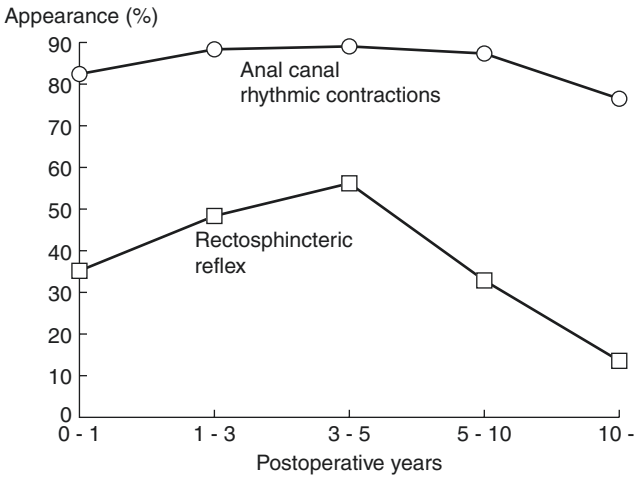

Fig. 28.5 Chronologic changes in the postoperative appearance of anal canal contractions and rectosphincteric reflex based on a manometric study. Cited from "Fig. 6" of Suita S, Taguchi T, Yanai K, Kamimura T, Nakao M, Ikeda K: Long-term outcomes and quality of life after Z-shaped anastomosis for Hirschsprung's disease. J Am Coll Surg. 1998 Dec;187(6):577–83

28.2.4 Barium Enema Study

Barium enema studies were done 226 times in 80 patients. The positive rates of megarectum, angulation, anal canal staining, and leakage were 41.1%, 88.3%, 23.3%, and 15.5%, respectively. Postoperative chronologic change in positive rates of megarectum and angulation is shown in Fig. 28.6. More than 80% of the patients constantly showed positive angulation, but megarectum tended to increase over time. The chronologic change of anal canal staining and leakage is shown in Fig. 28.7.

Table 28.1 Postoperative evacuative symptoms and manometric findings

Symptom		*n*	Rectal resting pressure (cm H_2O)	Anal canal resting pressure (cm H_2O)	Positive rate of anal canal rhythmic contraction (%)	Positive rate of rectosphincteric reflex (%)
Diarrhea	+	15	6.13 ± 3.85	35–20 ± 20.31	93	33
	–	17	5.06 ± 5–87	39.29 ± 24.11	88	20
Constipation	+	9	5.78 ± 3.46	42.11 ± 27.61	100	44
	–	23	5.48 ± 5–53	35–52 ± 20.03	86	26
Incontinence	+	16	7.31 ± 4.45[a]	40.63 ± 25.40	94	31
	–	15	3.53 ± 5–03[a]	33.47 ± 19.07	86	27
Soiling	+	19	6.16 ± 4.13	36.05 ± 25.64	89	16*
	–	13	4.69 ± 6.09	39.31 ± 16.56	92	54*

Cited form "Table 1" of Suita S, Taguchi T, Yanai K, Kamimura T, Nakao M, Ikeda K: Long-term outcomes and quality of life after Z-shaped anastomosis for Hirschsprung's disease. J Am Coll Surg. 1998 Dec;187(6):577–83

Table 28.2 Postoperative function of evacuation and the positive rate of rectosphincteric reflex

Function of evacuation	Positive rate of reflex (%)
Excellent	18
Good	54
Fair	0
Poor	0

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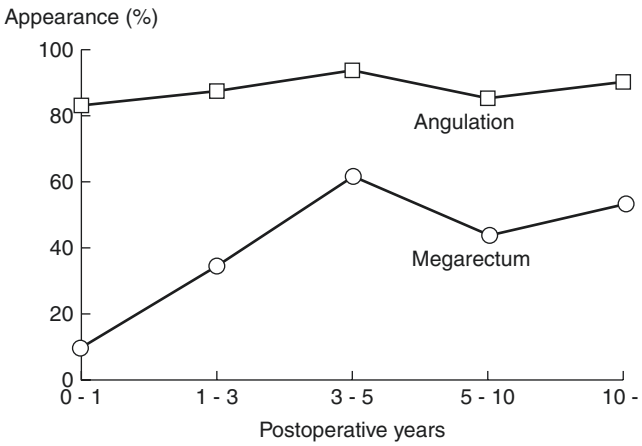

Fig. 28.6 Chronologic changes in the postoperative appearance of angulation and megarectum based on a barium enema study. Cited from "Fig. 7" of Suita S, Taguchi T, Yanai K, Kamimura T, Nakao M, Ikeda K: Long-term outcomes and quality of life after Z-shaped anastomosis for Hirschsprung's disease. J Am Coll Surg. 1998 Dec;187(6):577–83

The positive rate of these two parameters gradually decreased over time. The relationship between the symptoms and barium enema findings is shown in Table 28.3. Patients with constipation showed a high positive rate of megarectum, and patients with incontinence showed a low positive rate of megarectum. Patients with diarrhea or incontinence showed a high positive rate of anal canal staining and leakage, but no statistical significance was found between each parameter and symptom.

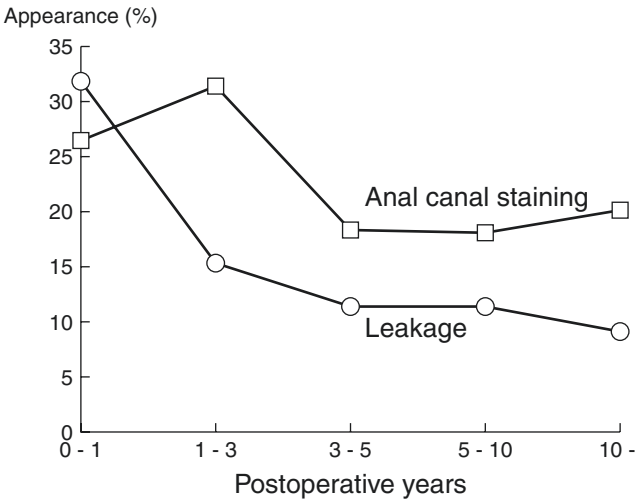

Fig. 28.7 Chronologic changes in the postoperative appearance of anal canal staining and leakage based on a barium enema study. Cited from "Fig. 8" of Suita S, Taguchi T, Yanai K, Kamimura T, Nakao M, Ikeda K: Long-term outcomes and quality of life after Z-shaped anastomosis for Hirschsprung's disease. J Am Coll Surg. 1998 Dec;187(6):577–83

Table 28.3 Postoperative evacuative symptoms and the barium enema findings

Symptom		*n*	Megarectum (%)	Angulation (%)	Anal canal staining (%)	Leakage (%)
Diarrhea	+	9	67	100	38	25
	–	14	50	93	14	7
Constipation	+	7	71	100	29	14
	–	16	50	93	20	13
Incontinence	+	9	33	88	38	25
	–	13	69	100	15	8
Soiling	+	13	62	100	8	8
	–	10	50	90	40	20

Cited from "Table 3" of Suita S, Taguchi T, Yanai K, Kamimura T, Nakao M, Ikeda K: Long-term outcomes and quality of life after Z-shaped anastomosis for Hirschsprung's disease. J Am Coll Surg. 1998 Dec;187(6):577–83

28.3 Long-Term Outcomes and the Quality of Life of Hirschsprung's Disease in Adolescents Who Have Reached 18 Years or Older

From 1963 to 2009, 184 patients with Hirschsprung's disease underwent definitive surgery mostly Ikeda-Z procedure at Kyushu University Hospital. As a result, 146 (95.4%) of 153 patients survived and reached 18 years of age. Their present status and symptoms, anorectal functions, genitourinary functions, and social performance were evaluated during the clinical follow-up using a questionnaire survey for these 146 patients. This study was based on personal interviews using a standardized format developed by two of the authors. The same questionnaire was sent by mail to the patients (n = 146). Responses were obtained from 43 (59.2%) of 71 patients excluding the 75 patients of address unknown. The status of evacuation was evaluated based on the following symptoms: diarrhea, constipation, incontinence, and soiling. Scoring was 2 points for none, 1 point for sometimes, and 0 points for always. A total of 7 to 8 points were estimated to be excellent, 5 to 6 points were good, 3 to 4 points were fair, and 0 to 2 points were poor [10]. This clinical study was performed according to the ethical guidelines of clinical research from Ministry of Health, Labor, and Welfare.

28.3.1 Background of Patients

The 42 patients included 35 males and 7 females. The extent of aganglionosis and the number of patients affected were as follows: lower rectum, aganglionosis restricted to the lower rectum under peritoneal reflection (n = 2); sigmoid colon, aganglionosis extended to the sigmoid colon (n = 32); left-right colon, aganglionosis extended beyond the sigmoid colon, but did not reach the cecum (n = 4); total colon, aganglionosis was limited to the total colon and 30 cm of the terminal ileum (n = 3); and small intestine, aganglionosis extended orally more than 30 cm of the terminal ileum (n = 1). Regarding the definitive operation, Ikeda-Z procedure was performed in 39 cases (92.9%). Swenson, Martin, and Lynn procedures were performed each one case. Age of patients is as follows: teenager is 2 patients (4.8%), 20s is 12 patients (28.6%), 30s is 17 patients (40.5%), 40s is 10 patients (23.8%), and 50s is 1 patient (2.4%). Median age is 33 years old (range, 19–55 years). Mean length of follow-up is 31 years.

28.3.2 General Status and Abdominal Symptom

The current status of body weight and height was available for all patients. Mean (SD) body weight is 64.8 (13.0) kg, and mean (SD) height is 168.2 (6.4) cm in the male patients. Mean (SD) body weight is 55.3 (12.3) kg, and mean (SD) height is 157.9 (8.9) cm in the female patients. The mean body weight and body height of Japanese who had reached 18 years old are 63.9 kg and 170 cm in the male and 56.7 kg and 158 cm in the female, respectively.

28.3.3 Status of Evacuation

As a result, 42 patients could be fully evaluated for this study, and the mean postoperative period was 31 years. A sense of defecation was present in 95.2% of the patients (Fig. 28.8a), and 92.8% of patients could discriminate the stool condition (Fig. 28.8b). The frequency of bowel movements and the time required for bowel movements are shown in Fig. 28.8c, d. The percentage of the patients who showed severe symptoms (0 point) was 9.5% for diarrhea, 4.8% for constipation, 0% for incontinence, and 4.8% for soiling. The percentage of patients who showed mild symptoms (1 point) was 45.3% for diarrhea, 33.3% for constipation, 19.0% for incontinence, and 11.9% for soiling (Fig. 28.9). The evacuation scores for all patients were as follows: excellent, 66.7%; good, 19.0%; fair, 11.9%; and poor, 2.4%. Therefore, 85.7% were considered to have a satisfactory bowel function (Fig. 28.10). However, only 21.4% had a full score of 8/8. Incontinence occurred in 16.7%, and soiling was reported by 19.0% of the questionnaire respondents.

28.3.4 Urinary Function

Five patients (11.9%) showed mild urinary complaints. Three patients showed frequent urination, and two had slight miction pain. Two of these patients had slight urinary incontinence. However, these symptoms were very mild and rare, and did not influence the social life of these patients.

28.3.5 Quality of Life

Nineteen (45.2%) of the 42 patients older than 18 years were married. Thirteen (68.4%) of 19 married patients had children. Fifty percent patients of married patients in their 20s had children, 62.5% of the married patients in their 30s had children, and 100% of the married patients in their 40s had children. The genital function of the married patients is considered to be favorable. The number of children was as follows: five patients had one child, four patients had two children, seven patients had three children, and two patients had four or more children. None of these children had Hirschsprung's disease. The definitive academic histories of the patients were as follows: 3 (7.1%) patients graduated

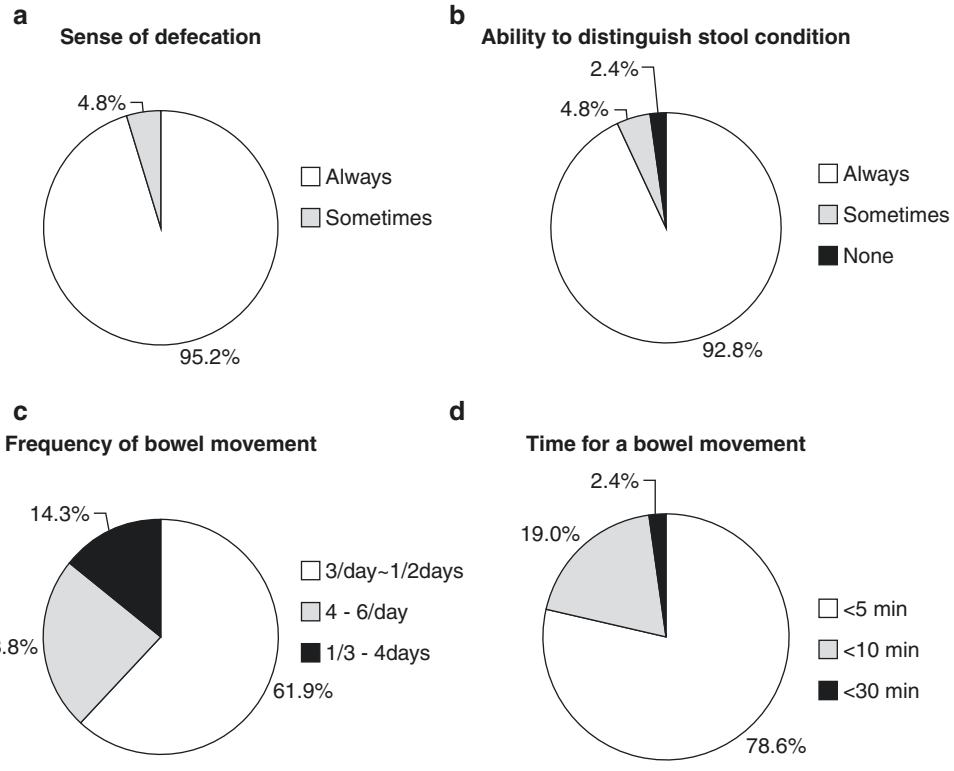

Fig. 28.8 Bowel function. Cited from "Fig. 1" of Ieiri S, Nakatsuji T, Akiyoshi J, Higashi M, Hashizume M, Suita S, Taguchi T (2010) Long-term outcomes and the quality of life of Hirschsprung disease in adolescents who have reached 18 years or older--a 47-year single-institute experience. J Pediatr Surg. 45:2398–2402

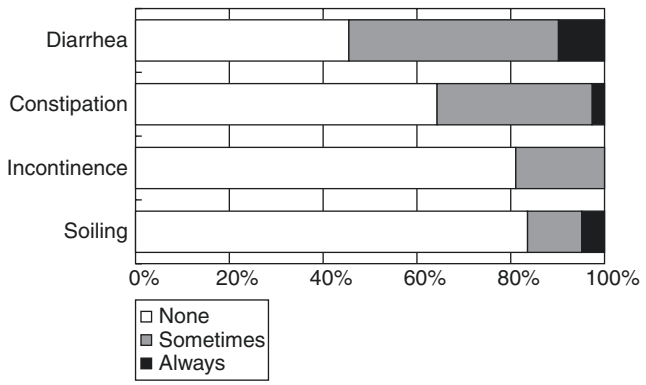

Fig. 28.9 Postoperative evacuative symptoms. Cited from "Fig. 2" of Ieiri S, Nakatsuji T, Akiyoshi J, Higashi M, Hashizume M, Suita S, Taguchi T (2010) Long-term outcomes and the quality of life of Hirschsprung disease in adolescents who have reached 18 years or older--a 47-year single-institute experience. J Pediatr Surg. 45:2398–2402

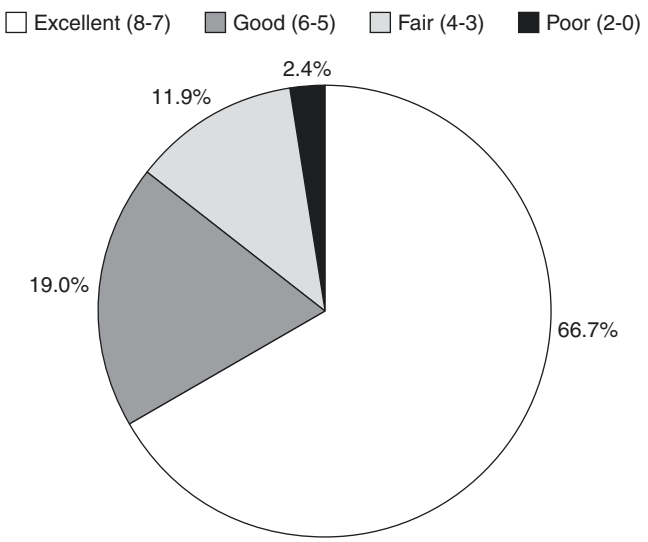

Fig. 28.10 Evacuation score. Cited from "Fig. 3" of Ieiri S, Nakatsuji T, Akiyoshi J, Higashi M, Hashizume M, Suita S, Taguchi T (2010) Long-term outcomes and the quality of life of Hirschsprung disease in adolescents who have reached 18 years or older--a 47-year single-institute experience. J Pediatr Surg. 45:2398–2402

from junior high school, 13 (31.0%) patients graduated from high school, 6 (14.3%) had professional school degree, 2 (4.8%) patients graduated from a junior college, 11 (25.6%) patients had a university degree, and 1 (2.4%) patient was conducting graduate research in a school of medicine. In Japan, the data of academic achievement in whole country population are as follows: high school degree, 25.3%; professional school degree, 18.2%; junior college degree, 7.1%; and university degree, 42.2%, respectively. Most patients appeared to be well-adjusted members of society, and 31 patients had regular occupations: nine were businessmen (21.5%), five were cooks (11.9%), three were engineers (7.1%), three were in the service industry (7.1%), one was in the bank business (2.4%), and one was self-employed (2.4%).

Six patients (14.3%) worked in healthcare professions: two were medical doctors, two were nurses, one was an occupational therapist, and one person worked as a member of the support staff at a facility for the physically handicapped. Three patients (7.1%) worked part-time, and four patients had no job. In addition, three patients were still in school.

28.4 Summary

Hirschsprung's disease is one of the representative functional disorders in pediatric surgery and has been considered to be curable by anastomosis of the normal ganglionic intestine to the anal canal by means of definitive surgery. In this chapter, we demonstrated the functional prognosis of Hirschsprung's disease in adolescents. The bowel function of postoperative state in Hirschsprung's disease in adolescents who reached 18 years or older was satisfactory. Regarding the social performance, they had reasonable academic backgrounds, and most had jobs and thereby positively contributed to society. Fecal continence improved significantly with age according to our previous report [10] and another report [11].

In the literature, Marty et al. [12] reported that 32% of such patients had fecal soiling, and 12.6% had severe symptoms out of 135 patients (Soave, 21%; Duhamel, 67%; Martin, 8%; myectomy, 4%; the mean length of follow-up was 7.9 years). Moore et al. [13] showed that 74.7% of the 115 patients older than 4 years had an excellent anorectal function and appeared to be well adjusted according to the functional assessment by three different scoring methods. However, they also reported that 19.2% had relatively minor long-term problems, but 6.1% had persistent fecal soiling, which thus had resulted in psychosocial maladjustment. Diseth et al. [14] reported that 32% of the adolescents with Hirschsprung's disease had a significant impairment of continence. Bai et al. [15] revealed that 23 patients (51.1%) had bowel dysfunction and 17 patients (37.8%) had fecal soiling in 45 patients after Swenson procedure. They also described that because of poor fecal continence, 25 patients (55.7%) had to restrict their diet and school absence occurred in 6 (13.3%) patients. Seven patients (15.6%) had problems in peer relationships.

In this way, incontinence and soiling during diarrhea impaired the quality of life in those patients. Constipation could be controlled using laxative and glycerin enemas like anorectal malformation, whereas incontinence and soiling are difficult symptoms to control. Regarding a patient's social life, frequent diarrhea in addition to incontinence and soiling might impair their qualities of life. However, the patients adjusted to these conditions and coexisted with these symptomatic states. These patients and their families always worry about stool odor. To prevent these complications, pediatric surgeons must carefully take this situation into consideration and attempt to modify the surgical procedures.

In the 1990s, minimally invasive techniques using laparoscopic procedures [16] and transanal endorectal pull-through [17] were introduced for the definitive operation of Hirschsprung's disease. These operative procedures offered either minimal scars or no scars on the abdomen of the patients, and it thus improved the quality of life in that way. However, the improvement of the anorectal function in the patients treated by these procedures should be evaluated for an extended period.

In conclusion, the function for evacuation in patients undergoing Ikeda-Z procedure improved chronologically. The appearance of a sense of defecation and an increase in the pressure difference between the anal canal and the rectum are thought to play a role in the chronologic improvement of the defecation score. In addition, pediatric surgeons should continue trying to achieve a complete bowel function after definitive surgery for the treatment of Hirschsprung's disease because incontinence and soiling clearly impair the quality of life.

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Long Term Result of Soave-Denda Procedure

29

Kazuhiko Nakame, Shun Onishi, Keisuke Yano, Toshio Harumatsu, and Takafumi Kawano

29.1 Introduction

Hirschsprung's disease has been one of the main disorders in pediatric surgical patients for a long time. The essence of treatment for Hirschsprung's disease is surgery. The classic operation was an abdominoperineal pull-through in two or three stages, in which patients initially underwent a diverting colostomy or enterostomy, and a definitive operation performed later. Various procedures have been developed to perform a definitive operation for Hirschsprung's disease including the Swenson procedure ([1]), the Rehbein procedure [2], the Duhamel procedure [3], and the Soave procedure [4].

In 1995, Georgeson et al. [5] reported minimally invasive procedure using transanal mucosectomy and primary laparoscopic pull-through. The one-stage transanal approach was developed by de la Torre et al. [6] in 1998. Thereafter, modification of the Soave procedure and transanal endorectal pull-through procedure was reported: Saltzman et al. [7] reported the modification of transanal mucosectomy in 1996, and Langer et al. [8] reported transanal one-stage Soave procedure for infants in 1999. Recently, most institutions choose one-stage procedure for a typical Hirschsprung's disease. Transanal endorectal pull-through was the most popular operation (49.6%) between 2008 and 2012 in Japan [9].

The postoperative outcomes of surgically treated Hirschsprung's disease are generally safe and satisfactory [10, 11]; however, the long-term outcomes in patients who underwent the modified Soave procedure or the TA approach are unknown.

In our institution, the Soave-Denda procedure [12] (SD procedure: modified Soave procedure, a primary coloanal anastomosis was described by Denda [13]) was applied for Hirschsprung's disease in the past. Since 1998, we changed the approach from transabdominal to transanal (TA), including laparoscopic-assisted. Despite the difference in approach, the concept of operative technique was not changed, such as the mucosectomy level and treatment of muscle cuff. In our institution, 110 Hirschsprung's disease patients underwent definitive diagnosis and operation from 1984 to 2015. The extent of aganglionosis was as follows: short segment type (ultrashort and rectosigmoid), 87 (79.1%); long segment type, 19 (17.4%); total colon aganglionosis with or without small intestine involvement, 3 (2.8%); and unknown, 1 (1.0%). The operative procedures performed were as follows: SD, 71 (64.5%); TA, 38 (34.5%); and Duhamel, 1 (1.0%) over the past 30 years.

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29.2 Long-Term Outcome of Hirschsprung's Disease: Comparison of the Abdominal Approach with Transanal Approach

In our institution, Onishi et al. [14] evaluated the long-term postoperative function of the general condition and bowel function in 106 consecutive cases (SD, 69 cases; TA, 37 cases, including 17 cases of laparoscopic-assisted) of patients who had undergone definitive operations using the SD procedure or the TA procedure for the short segment type of Hirschsprung's disease over the past 30 years. We report long-term results of Hirschsprung's disease as follows and add discussion from literatures.

29.2.1 Bowel Function Using the Evacuation Score

Onishi et al. [14] reported the bowel function data for patients older than 3 years of age were analyzed retrospectively in patients who underwent the SD or TA procedure. The bowel function was evaluated according to the evacuation score (ES) of the Japan Society of Anorectal Malformation Study Group

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Table 29.1 Evacuation score of the Japan Society of Anorectal Malformation Study Group

Parameter	Criteria	Score
Frequency of bowel movement	Frequent	2
	Accidental	1
	Absent	0
Constipation	Absent	4
	Accidental	3
	Requirement for enema or suppository everyday	2
	Requirement for colonic irrigation or stool extraction	1
Incontinence	Absent	4
	Incontinence with diarrhea	3
	Accidental	2
	More than twice a week	1
	Frequent	0
Soiling	Absent	2
	Accidental	1
	Frequent	0

in 1980 (Table 29.1) at 3, 5, 7, 9, and 11 years of age. The total scores were analyzed with the sum of frequency of the bowel movement score and soiling score. Regarding constipation and incontinence, a lower score is selected. The maximum score is 8 points, which indicates an excellent bowel function. A total of 7 to 8 points was estimated to be good, 4 to 6 points fair, and 0 to 3 points poor. In the series of Onishi, the mean total ES for each age was as follows: 3-year-old (SD 5.37 ± 1.89 vs. TA 4.63 ± 2.86, $p = 0.18$), 5-year-old (SD 6.30 ± 1.46 vs. TA 6.10 ± 1.97, $p = 0.64$), 7-year-old (SD 6.45 ± 1.57 vs. TA 6.25 ± 2.18, $p = 0.73$), 9-year-old (SD 6.97 ± 1.23 vs. TA 5.71 ± 2.63, $p = 0.05$), and 11-year-old (SD 7.35 ± 0.98 vs. TA 6.20 ± 2.17, $p = 0.07$). The total ES increased chronologically in both groups, and patients achieved satisfactory results at least 10 years after operation (Fig. 29.1). There was no significant difference in the total score between the TA and SD groups. The bowel function significantly improved with age in both the TA and SD groups, similar to the results of previous reports [15, 16]. Twenty-three of 28 (82.1%) patients who reached 11 years of age mostly achieved satisfactory bowel function. Neuvonen et al. [17] reported the bowel function in 57 cases of patients older than 4 years after transanal endorectal pull-through for Hirschsprung's disease using bowel function score by questionnaires.

The bowel functional outcome was good in 63% of patients and 96% of controls ($p < 0.001$), moderate in 26% of patients and 4% of controls ($p < 0.001$), and poor in 11% of patients and no controls ($p < 0.001$). The mean BFS was significantly lower in patients than in controls, although the mean BFS significantly improved with increasing age.

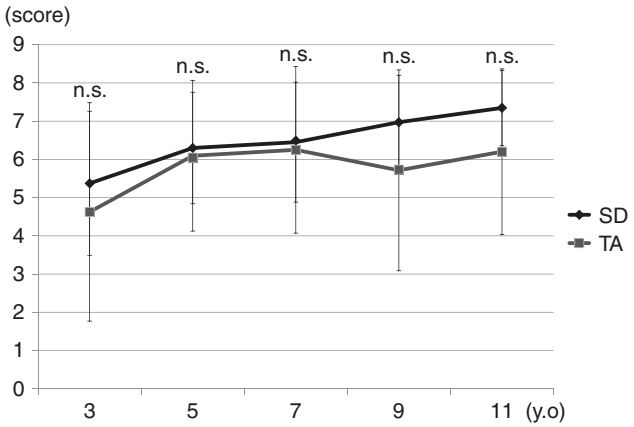

Fig. 29.1 Total evacuation scores. *n.s.* not significant

Bjørnland et al. [18] reported long-term bowel function in 200 patients with rectosigmoid Hirschsprung's disease after transanal endorectal pull-through was assessed using a bowel function score questionnaire in Nordic multicenter survey; only 73/200 (37%) patients reported absolutely no impaired bowel function. Tang et al. [19] reported their 10-year experience with the laparoscopic-assisted endorectal Soave pull-through procedure. The postoperative bowel function outcomes were excellent to good in 158 of 182 patients (87%) according to the Wingspread score, with a follow-up ranging from 6 to 120 months.

29.2.2 Frequency of Bowel Movement

Onishi et al. [14] reported that the frequency of bowel movement score at 7 years of age was significantly lower in the TA group than the SD group ($p < 0.05$) (Fig. 29.2). However, in both groups, patients (82.1%) who reached 11 years of age achieved a satisfactory bowel function. In the report of Neuvonen et al. [17], abnormal stooling frequency persisted in 50% of patients into adulthood. Teitelbaum et al. [10] reported the 1036 ± 614-day follow-up of 24 infants who underwent primary endorectal pull-through. Stooling frequency immediately after the operation was five to eight bowel movements per day, which declined to a mean of 3.8 ± 1.4 bowel movements at 6 months. And number of bowel movements per day declined to 2.7 ± 1.5 after l-year follow-up. The frequency of stool has a steep decline within the first 3 months after endorectal pull-through procedure. On the other side, Bjørnland et al. [18] reported the majority had more than two bowel movements per day and age was not associated with frequency of bowel movements.

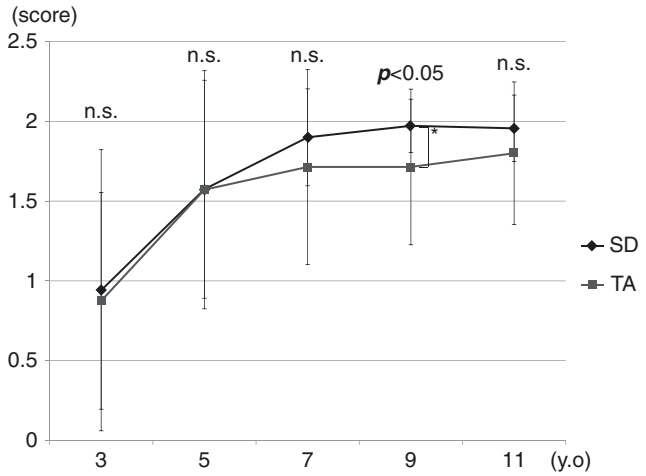

Fig. 29.2 Frequency of bowel movement score. *n.s.* not significant

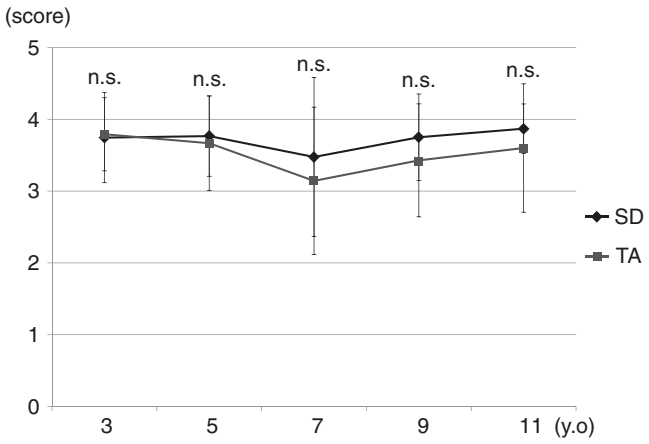

Fig. 29.3 Constipation score. *n.s.* not significant

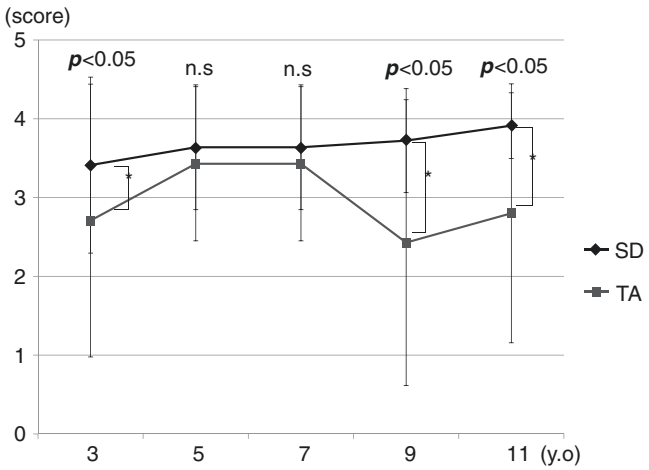

Fig. 29.4 Incontinence score. *n.s.* not significant

29.2.3 Constipation

Figure 29.3 shows the constipation score in our group [14]. About constipation, it showed satisfactory results, and there were no significant differences by age and the operative method. In the series of Teitelbaum et al. [10], there were 12 patients over 3 years of age with primary endorectal pull-through, and constipation was reported in 5 of the 12 children (42%). However, constipation was mild in most patients. Bjørnland et al. [18] reported 177 patients over 4 years with follow-up results of bowel function after transanal endorectal pull-through with rectosigmoid Hirschsprung's disease, and constipation was reported in 44 patients (25%) and was more common in the youngest patients. Zimmer et al. [20] reviewed 316 patients with the average follow-up of 4.3 years after transanal pull-through for Hirschsprung's disease. Twenty-four (53.3%) patients experienced constipation. Tang et al. [19] reported postoperative results of 182 patients, follow-up ranging from 6 to 120 months of laparoscopic-assisted endorectal Soave pull-through for Hirschsprung's disease. Constipation rate was 1.6%.

29.2.4 Incontinence/Soiling

Fecal incontinence was the most common problem for Hirschsprung's disease. In the series of Onishi et al. [14], the incontinence score at 3, 9, and 11 years of age was significantly lower in the TA group than the SD group ($p < 0.05$ for all) (Fig. 29.4). In both groups, 23 of 28 patients (82.1%) who reached 11 years of age mostly achieved a satisfactory bowel function. About the soiling score, there were no significant differences by age and the operative method (Fig. 29.5). Bjørnland et al. [18] reported soiling and fecal accidents were 77% of the patients and were less common among the older patients. Teitelbaum et al. [10] reported accurate history of continence of patients that 12 children were over 3 years of age, and continence was graded as good in nine of patients (75%), normal in one (8.3%), and fair in two patients (16.7%). Soiling was seen in the two patients (16.7%). Zimmer et al. [20] reported 8/316 (17.8%) patients experienced incontinence/soiling after transanal pull-through.

It has been thought with the transanal pull-through procedure that was low minimally invasive procedure. However, in the experience of our institution, incontinence score was

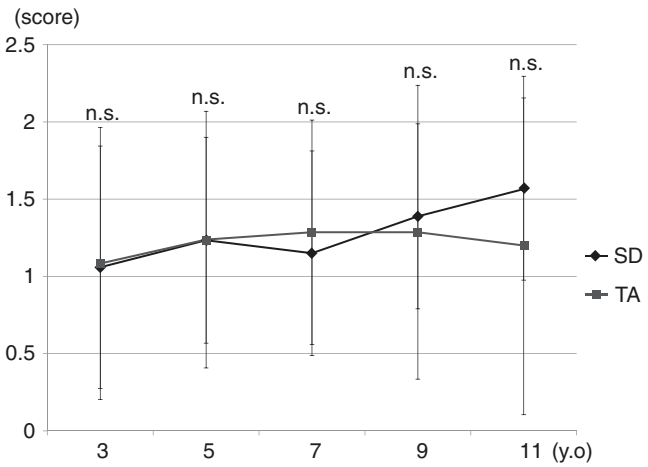

Fig. 29.5 Soiling score. *n.s.* not significant

significantly lower in the transanal group than in the SD group. Bjørnland et al. [18] reported transanal pull-through procedure was significantly associated with poor outcome. Onishi et al. [14] hypothesize two potential explanations: the superficial external anal sphincter muscle was excessively stretched and damaged during anal canal dilatation of transanal approach; or the deep external anal sphincter muscle and neurovascular band were directly damaged due to deep mucosectomy extending into the whole layer. Banerjee et al. [21] reported the functional consequences of transanal endoscopic microsurgery. As a result of dilation of the anal canal by the proctoscope and the prolonged operative time, it has been suggested that damage to the anal sphincter could cause postoperative fecal incontinence. Stensrud et al. [22] reported the study was to examine the anal sphincters by anal endosonography and manometry after transanal endorectal pull-through, with or without laparotomy or laparoscopy, in 52 Hirschsprung's disease patients. Endosonographic internal anal sphincter defects were significantly found more frequently after transanal than transabdominal procedures (69% vs. 19%). Daily fecal incontinence significantly occurred more often in patients with internal anal sphincter defects (54% vs. 25%). Mucosectomy from the anal side requires a dilated external sphincter muscle, and this manipulation could be the cause of damage due to overstretching of the muscle. To prevent anal sphincter muscle damage, pediatric surgeons must carefully take this situation into consideration and manipulate the muscle as gentle as possible.

Incontinence is thought to be less common following Duhamel procedure. Urushihara et al. [23] reported the outcome of the laparoscopic-modified Duhamel procedure with Z-shaped anastomosis. Twenty-six children with rectosigmoid Hirschsprung's disease underwent this procedure, and all patients older than 4 years of age achieved normal defecation without fecal incontinence. However, their data were only based on short-term results; therefore, the long-term results must be evaluated.

Onishi et al. reported patients with trisomy 21 only showed poor results due to incontinence and soiling. And another reported persistent bowel dysfunction was common in patients with trisomy 21 and Hirschsprung's disease [24, 25].

29.3 The Bowel Function and Quality of Life of Hirschsprung's Disease Patients for Adolescents and Adults

In our institution, from 1984 to 2016, 110 patients with Hirschsprung's disease underwent definitive surgery with the SD procedure and the transanal procedure (included laparoscopic-assisted surgery). We evaluated the long-term postoperative function of the bowel function and quality of life in patients ≥18 years of age who had undergone definitive operations for Hirschsprung's disease. Their present status and symptoms, anorectal functions, genitourinary functions, and quality of life were evaluated during the clinical follow-up using a questionnaire survey (Table 29.2) for these 63 patients. The same questionnaire was sent by mail to the patients ($n = 63$), and responses were obtained from 16 (25.4%). Sixteen patients were evaluated for this study, and the mean postoperative period was 24.6 years. The bowel function was evaluated according to the evacuation score (Table 29.1).

Table 29.2 Questionnaire

1.	How often do you become ill?
	• No
	• Sometimes
	• Always
2.	How is your appetite?
	• Good
	• Average
	• Bad
3.	Do you have nausea?
	• No
	• Sometimes
	• Always
4.	Do you have abdominal pain?
	• No
	• Sometimes (once or twice a week)
	• Every day
5.	Can you distinguish stool condition?
	• Always
	• Sometimes
6.	How many times do you defecate?
	• 3/days to 1/2 days
	• 4–6/day
	• 1/3 to 4 days

Table 29.2 (continued)

7.	How much time is required to long time was you required to defecate?
	• Less than 5 min
	• 5–10 min
	• 10–30 min
8.	Do you have pain when you defecate?
	• No
	• Sometimes (once or twice a week)
	• Every time
9.	What types of daily medication do your take?
	Do you have daily use medicine?
	• None
	• Antiflatulent
	• Enema
	• Suppository
	• Laxative
10.	Do you have diarrhea?
	• No
	• Sometimes (once or twice a week)
	• Every day
11.	Do you have constipation?
	• No
	• Sometimes (once or twice a week)
	• Every day
12.	Do you have incontinence?
	• No
	• Less than once a month
	• Sometimes (once or twice a week)
	• Often (more than twice a week)
	• Only when you have diarrhea
	• Every day
13.	Do you have soiling?
	• No
	• Sometimes (once or twice a week)
	• Every day
14.	Do you have urinary symptoms?
	• No
	• Frequent urination
	• Urinary pain
15.	Are you married?
	• Yes
	• No
16.	How many children do you have?
17.	What is your occupation?

29.3.1 Status of Evacuation

Figure 29.6 shows the bowel function of 16 patients ≥18 years of age who had undergone Soave-Denda procedure for Hirschsprung's disease in our group. A sense of defecation was present in 93% of the patients (Fig. 29.6a), and 87% of patients were able to discriminate the stool condition (Fig. 29.6b). The frequency of and time required for bowel movements are shown in Fig. 29.6c, d. Figure 29.7 shows the evacuative symptoms of patients, 88% of the patients had diarrhea, 31% of the patients had constipation, 19% of the patients had incontinence, and 19% of the patients had soiling. Regarding pain symptoms, 56% of patients had abdominal pain more than once a week. The evacuation scores for all patients were good in 81% of patients, fair in 19% of patients, and poor in 0% of patients. Eleven patients (69%) had a full score of 8/8. The total bowel function in postoperative Hirschsprung's disease patients was almost satisfactory. Incontinence occurred in 19% and soiling occurred in 19% of the questionnaire respondents.

Previous articles Ieiri et al. [16], Suita et al. [26], and Teitelbaum et al. [10] reported the bowel function improved significantly with age; however, in our series, these complications remained in 19% of patients. A few patients who had reached adulthood were still suffering from chronic symptoms. Bjørnland et al. [18] reported that among the teenagers and adults, 93% experienced no fecal accidents or fecal accidents less than once a week as opposed to 76% in those below 13 years. In the series of Neuvonen et al. [17], 29% of patients over 4 years of age had social problems due to functional bowel symptoms. And above age 18 years, patients continued to report more social problems, and difference was no longer statistically significant.

29.3.2 Urinary Function

No patients had any urinary complaints, such as slight urination pain or urinary incontinence. The advantage of the Soave-Denda procedure is that the perirectal tissue remains protected; as such, this procedure can avoid damaging the major urogenital nerve structures and pelvic veins that regulate the genitourinary function. In the series of Ieiri et al. [16], 5/42 (11.9%) patients who underwent the modified Duhamel procedure showed mild urinary complaints and the following symptoms: frequent urination, slight miction pain, and slight urinary incontinence. However, these symptoms were very mild and rare and did not influence the social life of these patients. Neuvonen et al. [27] reported that no significant differences were demonstrated in the overall prevalence of lower urinary tract symptoms between patients ≥4 years of age who underwent the endorectal pull-through and controls. Further discussions comparing the urinary function among each procedure are necessary in the future.

29.3.3 Quality of Life

Regarding to the quality of life of 16 patients ≥18 years of age in our group, the definitive academic histories of the patients were as follows: 1 (6%) patient had graduated from junior high school, 3 (19%) had graduated from high school, 4 (25%) had a professional school degree, 1 (6%) had gradu-

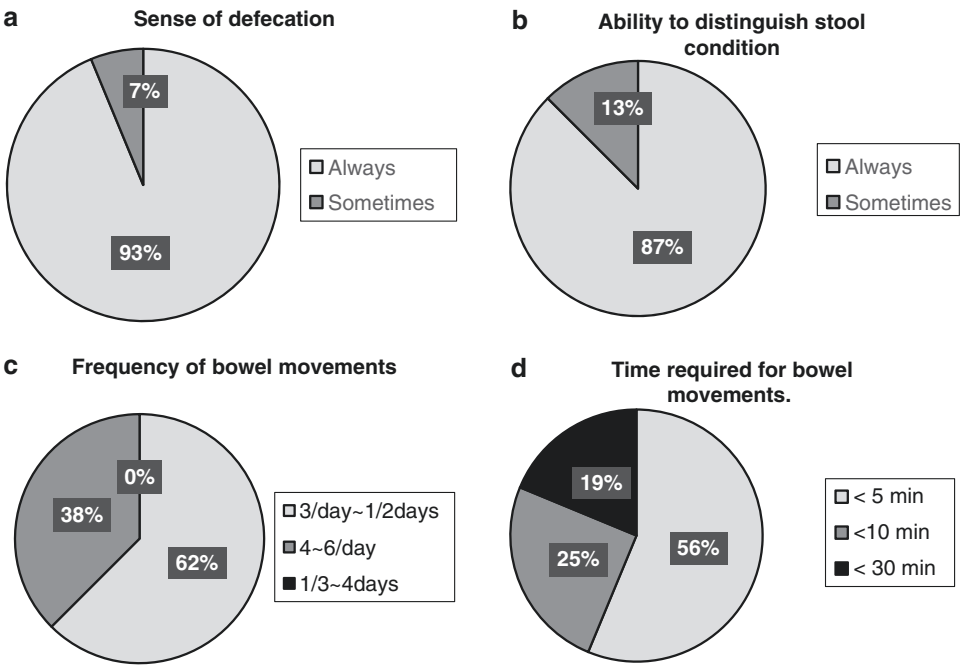

Fig. 29.6 Bowel function of patients ≥18 years of age

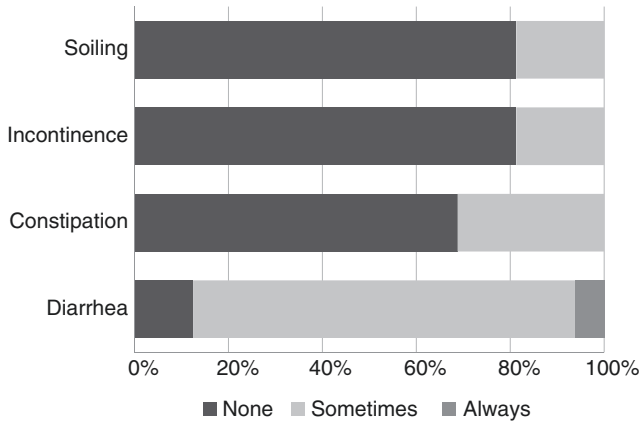

Fig. 29.7 Postoperative evacuative symptoms of patients ≥18 years of age

ated from a junior college, and 7 (44%) had the university degree. In Japan, the data for academic achievement among the national population are as follows: high school degree, 25%; professional school degree, 18%; junior college degree, 7%; and university degree, 42%.

Most patients appeared to be well-adjusted members of society, and ten patients had regular occupations: five were businessmen (31%), and one was an engineer (6%). Four patients (25%) worked in health-care professions: two were nurses, one was a physical therapist, and one was a clinical nutrition manager. One patient (6%) worked part-time, and two patients had no job. In addition, three patients were still in school.

Five (31%) of the 16 respondents were married. Three (60%) of the five married patients had children. The genital function of the married patients was considered to be favorable. The number of children was as follows: one patient had one child, one patient had two children, and one patient had three children. One of these children also had Hirschsprung's disease. In the present study, 60% of the married patients had more than one child, and the genital function that was thus considered seems to be favorable. However, our questionnaire did not include any other questions about other sexual health, and there were not enough cases to draw any restrictive conclusions.

Ieiri et al. [16] reported the long-term outcomes and the quality of life of adult Hirschsprung's disease patients who had undergone the modified Duhamel procedure (Z-shaped anastomosis, open approach). Among the 42 respondents older than 18 years, 19 patients (45.2%) were married, and 13 patients (68.4%) of those married had children. Neuvonen et al. [27] reported the assessment of the sexual function after endorectal pull-through. Twenty-four patients ≥16 years of age responded to the questions on their sexual function, including the assessment of erectile function in males. Male patients reported sexual satisfaction and erectile function similar to control. Female patients were currently less in stable relationships compared to controls (25%; n = 2/8 vs. 83%; n = 20/24). Moore et al. [28] reported postoperative sexual dysfunction among Soave, Duhamel, and Swenson procedures that were 3/55 (1%), 4/21 (9%), and 6/13 (10%) of the patients, respectively. However, the mean follow-up age of patients is 10 years.

Some authors reported the long-term follow-up outcomes of Hirschsprung's disease after each procedure [29–31]. However, the median follow-up periods of these reports were under 10 years in most cases, and the studies focused on only the bowel function. Only a few reports have evaluated the social performance and quality of life of adolescent patients who underwent definitive surgery [16, 17, 32]. There is the limitation of our results without enough any evaluations of the emotional condition of the patients with Hirschsprung's disease. The patients with Hirschsprung's disease may endure many diagnostic procedures, operations, and hospital admissions during childhood. And the patients with Hirschsprung's disease may have problems with fecal continence, urinary continence, and sexual function. These problems may affect children in the form of an impaired emotional psychosocial health. Neuvonen et al. [17] found that patients 8–18 years of age reported a normal quality of life overall despite significant impairment of fecal control. Interestingly, the scores in patients were even higher in the emotional and social subscales in matched controls. Witvliet et al. [33] reported 27 patients (17 anorectal malformations and 10 Hirschsprung's disease, mean age 27.9 years (range 17–64 years)) found that the overall quality of life was not influenced by disease-specific function, and the transitional outpatient clinic provides care adapted to the needs and wishes of adult patients. Our date has the limitations because of the low response rate. The advantage of the Soave-Denda procedure (including transanal endorectal procedure) for Hirschsprung's disease is that the perirectal tissue remains protected. However, long-term bowel function and the results of the quality of life (e.g., social problems, emotional problems, urinary function, and genital function) remain unknown. Long-term follow-up is necessary to evaluate these outcomes in adulthood.

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Redo Pull-Through and Secondary Operation

30

Miyuki Kohno

30.1 Introduction

The most common techniques nowadays for Hirschsprung disease (HD) are a transanal approach with or without laparoscopic assistance, a modified Soave procedure, Duhamel procedure, and the Swenson procedure. Although these procedures have been considered to lead to good results, various authors have reported postoperative complications in some children and the need for a secondary operation or redo pull-through to treat severe complications in others, regardless of the approach. Complications after pull-through will greatly affect the quality of life of children with HD. If conservative management of complications is unsuccessful, surgical therapy should be considered.

The incidence of secondary operation or redo pull-through in postoperative HD cases is unclear because there are few relevant accurate reports in the literature. Pini-Prato et al. [1] reported the prevalence of reoperation in their institution as 1.1%. Kim et al. [2] reported that the incidence of redo pull-through was higher for the transabdominal approach (11%) than for transanal endorectal pull-through (TERPT) (1%). In a meta-analysis, Zimmer et al. [3] reported that 3.2% of all patients who underwent transanal pull-through (TAPT) developed complications requiring a secondary operation, with the majority needing redo surgery. Ralls et al. [4] reported an incidence of 2% redo pull-through in children from their own group of primary pull-through cases.

This chapter focuses on the etiology of postoperative complications and the indications for secondary or redo operation. It is obvious that successful treatment cannot be achieved unless the cause of complications is evident.

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30.2 Evaluation of Postoperative Complications and Determination of Treatment

If a patient suffers postoperative complications, evaluation to determine the treatment plan should be conducted as follows: detailed operative course, physical examination (rectal examination is essential), radiographic water-soluble contrast enema, anorectal manometry, and rectal biopsy. It is important to identify the etiology of complications. The results of these evaluations will influence the decision on whether to undertake a secondary operation and whether redo pull-through will be necessary.

Anal appearance is important in indicating the defecation status and anal canal function. A patient with a patulous anus might also have a damaged anal canal. Rectal examination is essential to help locate the presence of an anastomotic stricture, the presence of narrowing caused by Soave cuff, the status of the sphincters, or the presence of a large rectal pouch via Duhamel procedure. If necessary, examination of the anal canal should be performed under anesthesia to determine whether the anal canal or dentate line is intact or disrupted.

A contrast enema can reveal anatomical change after a radical operation and provide information about any structural anomalies that may account for the patient's complications. This may show two characteristics: a nondilated colon or a dilated colon. A nondilated colon might be found in patients with complications but without obstructive symptoms. A contrast enema may show a dilated colon in patients with complications characterized by obstructive symptoms. Based on this appearance, we can distinguish between pseudoincontinence and true fecal incontinence [5]. If a patient with soiling and a dilated colon on a contrast enema has an intact anal canal and internal sphincter, (s)he might have pseudoincontinence. If a patient has a damaged anal canal and a damaged internal sphincter, (s)he will be unable to retain contrast material in the rectum. Such a patient would have true fecal incontinence.

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Rectal biopsy is the most important tool for evaluation of late obstructive symptoms after pull-through because the causes of obstructive symptoms requiring redo pull-through are most frequently attributable to residual aganglionosis and transition-zone bowel [4, 6]. A four-quadrant biopsy should be considered to exclude partial circumferential aganglionosis. It is also preferable to conduct full-thickness rather than suction biopsies [7].

Anorectal manometry may be useful in identifying internal sphincter achalasia and a damaged anal canal. Increasing or decreasing anal resting pressures will help to diagnose internal anal sphincter achalasia or a damaged anal canal. Anal endosonography [8] may be useful to evaluate the status of the external and internal anal sphincters.

30.3 Postoperative Complications After Pull-Through Procedure

Postoperative complications are classified into two types depending on the onset time: early complications and late complications [4]. Early and late complications after a pull-through procedure are listed in Table 30.1.

30.3.1 Early Postoperative Complications

Early complications include anastomotic leak, which may cause a fistula formation, and obstructive symptoms after pull-through, mostly due to mechanical obstruction such as anastomotic stricture, twisted pull-through segment, obstruction of Duhamel pouch, and Soave cuff. The causes of early complications, all of which require reoperation, are related to gross anatomical problems [4]. Ralls et al. [4] reported early complications occurring in 44% of all cases that eventually underwent a redo pull-through.

Routine radiographic contrast enema of anastomosis should be done 2 weeks after the initial operation, even if there is no change in the general condition of the patient. This enema can reveal the presence or absence of anastomotic leak, anastomotic stricture, and twisted pull-through segment. If anastomotic leak is recognized, colostomy may be considered. Anastomotic stricture or rectal muscular cuff-related narrowing can be managed by repeated dilatation. If obstructive symptoms due to a twisted pull-through segment are recognized, immediate surgical revision is necessary.

Table 30.1 Postoperative complications

Early complications	Late complications
• Obstructive symptoms	• Obstructive symptoms
Mechanical obstruction	Mechanical obstruction
Stricture	Pathologic problem
Twisted pull-through segment	Residual aganglionosis
Duhamel pouch	Transitional zone
Soave cuff	Internal sphincter achalasia
• Others	• Fecal incontinence
Anastomotic leak/abscess	Damaged anal canal
	Damaged sphincter function
	• Others

30.3.2 Late Postoperative Complications

Late complications comprise two groups: obstructive symptoms and fecal incontinence. Most Hirschsprung disease-associated enterocolitis is related to obstructive symptoms. Rintala and Pakarinen [9] reported that approximately one-half of these patients have impaired bowel function mainly resulting from different degrees of fecal incontinence and constipation.

Graström et al. [10] reported that the constipation rate decreases over time, although the soiling rate remains very high and tends to persist. However, there are reports [11, 12] that fecal symptoms or fecal control improves significantly with age after TERPT.

It is important to identify the necessity of reoperation in late complications.

30.3.2.1 Obstructive Symptoms

Obstructive symptoms include abdominal distension, bloating, vomiting, and constipation. Constipation is the most common postoperative complaint after a pull-through in any radical procedures for HD. The incidence of obstructive symptoms after a pull-through procedure varies considerably from 5% to 42% in the literature [9, 13]. According to Tomuschat et al. [14], 11.8% of patients had constipation in a meta-analysis of laparoscopic-assisted pull-through by several techniques. Zimmer et al. [3] reported an incidence of constipation after pull-through procedure of 7.6% among 316 patients in a meta-analysis of long-term results of TAPT.

The timing of obstructive symptoms is variable. The reasons for obstructive symptoms after a pull-through may be either anatomically or pathologically related [15]. The etiology of anatomical problems includes anastomotic stricture, Duhamel pouch, obstructive Soave cuff, retained dilated distal segment, and kink or twist of pull-through segment. Pathological problems include residual aganglionosis, acquired aganglionosis, transition-zone pull-through, internal anal sphincter achalasia, motility disorder, and functional megacolon due to stool-retaining behavior [7]. Late complications in those children eventually requiring a redo pull-through include obstructive symptoms (87%), of which functional constipation makes up the majority (54%) [4].

Dingemans et al. [16] reported that all of their patients who underwent redo pull-through surgery had obstructive symptoms. Friedmacher and Puri [6] found in their meta-analysis that one-third of all patients with HD requiring redo pull-through had residual aganglionosis and transition-zone bowel. The findings that residual aganglionosis and transition-zone bowel are responsible for the majority of problems highlight the importance of appropriate pathological evaluation of the pull-through segment during the initial operation [4]. Acquired aganglionosis might result from neuronal cell death after an ischemic insult on the distal pull-through or may arise from the child's natural body growth causing upward tension on the pull-through segment [17].

Anastomotic strictures or a narrowed Soave cuff can be managed with serial dilatation. If there are no anatomical problems, a rectal biopsy is required to verify normal innervation in the pull-through. If necessary, rectal biopsy should be repeatedly performed. If there is no mechanical obstruction and normal aganglionosis in the pull-through bowel, internal sphincter achalasia may be suspected. Botulinum toxin injection into the internal anal sphincter can be useful for the treatment of internal sphincter achalasia [7]. Internal sphincter myectomy or myotomy may be used for the child who responds well to botulinum toxin but subsequently experiences recurrent symptoms. Wildhaber et al. [18] reported moderate success for posterior myotomy/myectomy (POMM) to treat chronic constipation or recurrent enterocolitis in patients with HD after pull-through. They reported that 75% of patients in the enterocolitis group without or with aganglionosis became free of symptoms. The success rate of POMM among patients with constipation who had normal aganglionosis cells in the rectum was quite high (83%). The highest failure rate was found in the group with both constipation and aganglionosis of the lower rectum. Because of the unsuccessful outcome with POMM in patients with a combination of constipation and aganglionosis, one should defer to a redo pull-through for these patients. However, Langer et al. [7] reported that POMM carries a long-term risk of fecal soiling. They recommend a nonoperative approach, as most cases will resolve over time without surgical intervention, avoiding the risk of fecal incontinence.

Indications for Redo Pull-Through Operation for Obstructive Symptoms

If conservative management is unsuccessful, a secondary or redo pull-through operation should be considered.

Sheng et al. [19] classified the indications for reoperation into three groups: (1) anatomical problems, such as anastomosis stricture, twisted pull-through segment, retained dilated segment, obstructive Duhamel pouch, and obstructive Soave cuff; (2) pathological problems, e.g., residual aganglionosis and retained transition-zone bowel; and (3) other problems, e.g., HD-associated enterocolitis and fistula. Sometimes one child may have a combination of problems.

Ralls et al. [4] classified patients into three groups: the immediate reoperative group within 6 months after the primary pull-through, the early group (<3 years), and the late group (>3 years), according to the time interval between primary pull-through and redo pull-through. They reported that all patients operated on within 6 months after the primary pull-through had gross anatomical indications (twisted pull-though segment, obstructing Duhamel pouch, or stricture) for their redo pull-through. In the early group (<3 years) and late group (>3 years), 40% and 70% of patients had residual aganglionosis/transition-zone bowel, respectively.

When a surgeon is notified of a misread frozen section within a few days after the initial pull-through, an immediate repeat pull-through is recommended because of the possibility of fewer adhesions [20].

Dingemans et al. [16] reported the technique of the primary surgery as mainly TERPT (50%), followed by Rehbein (19%), Duhamel (19%), and Swenson-like TERPT (13%). Ralls et al. [4] reported the open endorectal pull-through as most frequently used for primary pull-through (41%), followed by TERPT (22%), Swenson (17%), Duhamel (11%), and unknown approach (9%).

According to Dingemans et al. [16], the time to remain on conservative management before deciding to perform redo surgery depends on the indication for redo surgery. They advocated that for all other cases except torsion of pull-through segment, conservative management was obligatory for at least 1 year, and only when this was considered unsuccessful for obstructive symptoms or incontinence (despite bowel management) would the possibility of surgical therapy be considered. The reason for waiting is that any additional scar fibrosis tends to subside in the first year and may be attributed to initial obstructive symptoms.

Procedure for Reoperation for Obstructive Symptoms

The choice of which procedure to use is far from being easy and obvious. Thus far there is no consensus and no best operative approach regarding the procedure for redo pull-through [4]. The patient's overall condition should be considered, including the type of previous failed procedure, level of anastomosis, rectal blood supply, and fibrosis or inflammation of the pelvis and perirectum. The redo operation carries risks far greater than the original surgery. The patient should be evaluated on an individual basis, and operative intervention should be planned according to presentation, type of complication, underlying pathology, and previous surgical history [4].

Sheng et al. [19] reported that the posterior sagittal approach combined with laparotomy has the advantage of excellent exposure and precise dissection under direct vision and has minimal impact on the pelvic nerves for those

patients with frozen pelvis or for those with a stricture or fistula located at a site not easily accessible, i.e., considered too low if approached from above or too high from below. Sun et al. [21] also reported posterior sagittal anorectal plasty as a useful alternative in difficult cases requiring redo pull-through surgery.

Sheng et al. [19] reported that during the redo Soave operation, mucosectomy was sometimes difficult and that sharp dissection was used at the level of previous anastomosis, especially after a Rehbein procedure. If unable to access the submucosal plane, conversion to a Duhamel procedure is a possibility.

Ralls et al. [4] reported carrying out many redo operations using open ERPT although Duhamel, Swenson, and transanal methods were also optional.

The transabdominal approach is preferred for cases with long-segment aganglionosis, twisted pull-through segment, or stricture due to ischemia or leak [3].

Success rates vary after redo pull-through depending on the definition of good outcomes. Peña et al. [22] reported soiling and fecal incontinence after redo surgeries (other than TERPT) for HD and also found a relatively high incidence of 27% (12 of 45 cases). Dingemans et al. [16] reported TERPT for redo surgery for HD as being effective in resolving sustained severe obstructive symptoms after primary surgery, although outcomes were complicated by a relatively high rate (43%) of soiling and fecal incontinence. Bischoff et al. [26] reported that the need for redo pull-through increased the risk of damaging the anal canal. Lawal et al. [23] reported that most patients (83%) had voluntary bowel movement after redo pull-through. Ralls et al. [4] reported that 81% of patients retained continence after redo pull-through.

Many reports describe the necessity of a protective colostomy or ileostomy to prevent recurrent fistula after redo pull-through [4, 16, 19].

All of these redo pull-through procedures, while technically challenging, are viable options for reoperative approaches to treat HD [4].

30.3.2.2 Fecal Incontinence

Incontinence rates have been reported at an incidence of 0–58.6% after a pull-through procedure [3, 9, 14, 24, 25]. These figures include patients with all degrees of incontinence. Some authors [14, 26] report that fecal incontinence after pull-through surgery is more frequent for Soave pull-through than for Swenson and Duhamel procedures. Stensrud et al. [8] reported that endosonographic internal anal sphincter defects were present in 24 of 50 patients (48%), more frequently after TERPT than after transabdominal procedures. They considered that internal anal sphincter defects contributed to fecal incontinence in many patients with HD. Tannuri et al. [27] evaluated the incidence of fecal incontinence and the quality of life of children with HD who underwent Duhamel or TAPT techniques and observed that impairment of quality of life was greater in patients who underwent TAPT rather than the Duhamel technique. Bischoff et al. [26] reported that of 103 patients with fecal incontinence after surgery, 54 had a damaged anal canal and 22 of these 54 patients also had a patulous anus. They reported that the Soave pull-through procedure was the most common operation in both groups: those with a damaged anal canal and those with an intact anal canal with fecal incontinence. However, Rintala and Pakarinen [9] reported that according to available evidence, there are no significant differences in the incidence of incontinence among different operative techniques over the long term [9].

The distinction between overflow pseudoincontinence and true incontinence is very important. Postoperative true fecal incontinence is a more serious problem that significantly reduces the quality of life of a child in comparison with obstructive symptoms. The suspected causes of true incontinence after pull-through are threefold: (1) the very low anastomosis causes a loss of anal canal sensation due to destruction of the sensory rectal mucosa; (2) the internal sphincters might be damaged by overstretching of the anus during the transanal procedure; and (3) the over-splitting of the internal anal sphincter due to myotomy prevents internal sphincter achalasia. Most true incontinence is thought to be caused by such damage to the anal canal. It is usually difficult to improve the health of patients presenting with true fecal incontinence and a patulous anus by bowel management alone.

To prevent postoperative fecal incontinence, it is important to avoid not only the low levels of anastomosis and excessive stretching of the anal canal during the operation but also excessive use of myotomy to prevent achalasia in the internal anal sphincter. Stensrud et al. [8] reported that fecal incontinence occurred more often in patients with internal anal sphincter defects. They hypothesize that the anal dilatation during the endorectal pull-through is an important contributor to the defects observed in the internal anal sphincter.

The damaged anal canal function and internal sphincter function should theoretically be preventable by careful surgical techniques.

Indications for a Secondary Operation for True Incontinence

To obtain a good outcome, most patients with true incontinence would have to forgo routine bowel management and move on to management with daily large-volume enema or be indicated for a Malone appendicostomy. Levitt et al. [28] reported that 42.6% (29/68) of patients with fecal incontinence after surgery for HD had true incontinence; of these patients, 20.6% (6/29) showed no improvement with a bowel

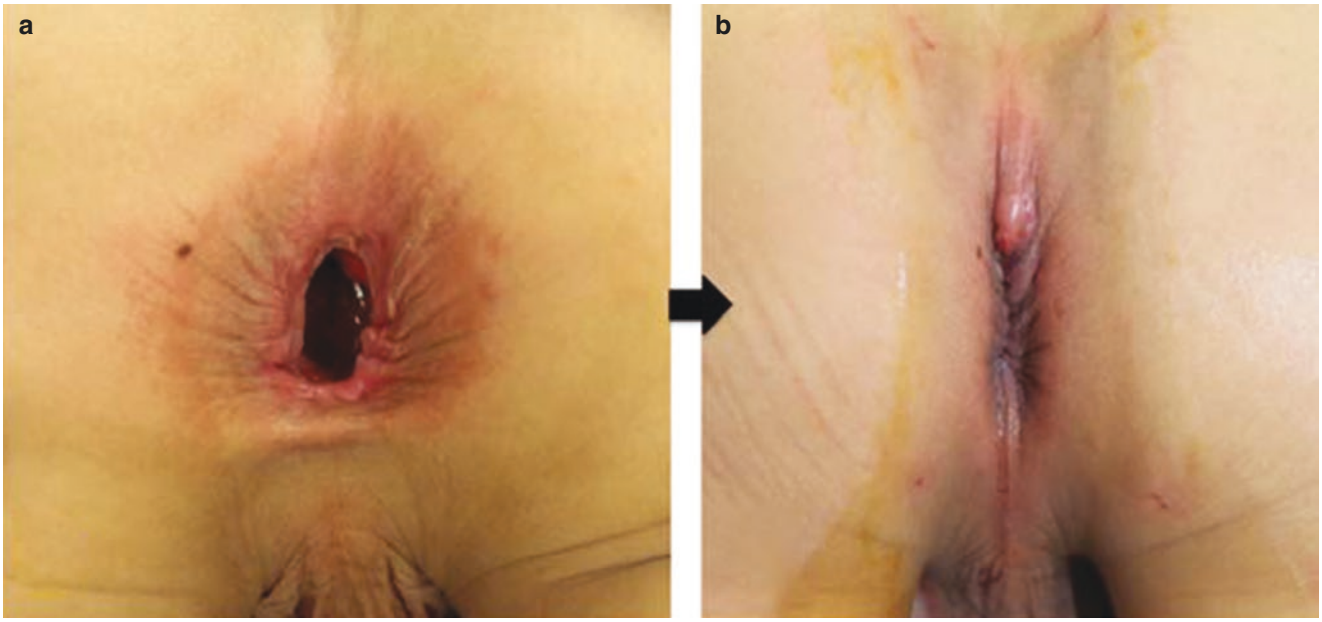

Fig. 30.1 (**a**) Patulous anus in jackknife position under general anesthesia in a child previously operated on for Hirschsprung disease. (**b**) Appearance of the anus after anal canal plasty

management program. However, there have been no reports of surgical repair for children with fecal incontinence after operative management for HD. Recently, Yasui et al. [29] reported that anal canal plasty might be effective for true incontinence with a patulous anus. Indications for anal canal plasty at reoperation are as follows: (1) patients with patulous anus at rest; (2) radiologically, no presence of fecal accumulation in colon and inability to retain contrast material in the rectum; and (3) severe fecal incontinence despite bowel management.

Secondary Operation for True Incontinence with Patulous Anus

Levitt et al. [30] described that the use of sphincter reconstruction can play a role, as has been used in other circumstances; however, the results of this procedure were not reported.

Yasui et al. [29] reported that anal canal plasty was effective for true incontinence with a patulous anus. They performed anal canal plasty for seven patients with a patulous anus, and all patients except one were able to retain the contrast material in their rectum after this procedure. Figure 30.1a shows a patulous anus under general anesthesia in a child previously operated on for HD, while Fig. 30.1b shows the anus after anal canal plasty. They considered that the rationale for the surgical procedure was to fold the posterior wall of the anal canal inward and hold it with interrupted stitches, leading to the creation of a valve mechanism in the anorectal junction. Additionally, after narrowing the anal canal and repairing the surrounding sphincter muscles, these sphincter muscles regain their function. Therefore, most patients were able to retain the contrast material in their rectum after anal canal plasty. This surgical approach may be a feasible treatment choice for true fecal incontinence in patients with a patulous anus.

30.4 Conclusions

Most of the postoperative complications discussed herein are preventable by careful pathological judgment and appropriate surgical procedure. The surgeon must understand the cause of each complication and plan the initial surgery with the aim of reducing each complication. Finally, when reoperation is deemed necessary for a child, the procedural approach most appropriate for each individual must be determined.

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Future Aspect

31

Sukhada Bhave and Ryo Hotta

31.1 Introduction

The enteric nervous system (ENS) consists of neurons and glial cells arranged in networks of ganglia within the wall of the gastrointestinal (GI) tract and regulates multiple critical aspects of gut function [1]. The ENS arises from neural crest cells that migrate along the developing GI tract. Enteric neuropathies, which are characterized by the congenital absence, acquired loss, or abnormal function of intrinsic enteric neuronal networks, represent some of the most severe clinical GI disorders. Hirschsprung disease (HSCR) is among the best understood of these. It is a congenital disorder of the ENS affecting 1 in 5000 children and is characterized by the absence of ganglion cells along variable lengths of distal bowel due to failure of neural crest-derived precursors to colonize the entire intestine [2, 3]. The aganglionic intestine is functionally obstructed, and treatment involves surgical resection of that segment. Surgery is lifesaving but often accompanied by long-term GI problems, including enterocolitis and fecal incontinence, which significantly reduce the quality of life of these patients as discussed in other chapters. Hence more effective and curative therapies for HSCR have been warranted. Recent advances in molecular biology and genetics have significantly enhanced our understanding of the development of the ENS [3, 4]. This has translated to identification of pathways involved in the pathogenesis of HSCR and development of novel tools for its treatment, such as cell-based therapy or regenerative approach to definitively restore ENS missing components [5–8]. In this chapter, we will summarize the remarkable progress that has been made and the challenges that remain in the development of potentially curative cellular therapies for HSCR. A set of key steps for clinical application of cell therapy to treat patients with HSCR is also proposed as a future aspect of treatment of HSCR.

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31.2 Cell-Based Therapies for Hirschsprung Disease: Background, Concepts, and Cell Sources

Cell therapy has successfully been performed for many years in the form of bone marrow transplants and is a potential treatment strategy for progressive neurodegenerative disorders of the central nervous system as well as neuronal degeneration secondary to other abnormalities and injuries [9, 10]. The use of cell replacement therapy in treating ENS developmental disorders has opened new avenues in regenerative medicine and has been actively investigated in light of the overall lack of effective therapeutic options for most of the enteric neuropathies, the accessibility to harvest donor cells as well as to deliver cells, and the possibility of autologous transplantation [5–8, 11]. Identifying an easily accessible, autologous, and reliable source of neural progenitor cells would address many of the current challenges and might be useful in the treatment of a wide range of neurologic disorders [7, 8]. Here, we discuss the most recent and exciting findings from two potentially autologous cell sources: endogenous ENS-derived enteric neural progenitor cells (ENPCs) and pluripotent stem cell (PSC)-derived ENPCs (Table 31.1).

31.2.1 Endogenous ENS-Derived Enteric Neural Progenitor Cells (ENPCs)

Arguably one of the most attractive cell sources for cell-based therapy for ENS disorders are derivatives of neural crest cells that specifically give rise to enteric neurons and glia, termed as “enteric neural progenitor cells” (ENPCs). During embryogenesis, a group of cells from neural crest migrates along defined pathways to give rise to diverse structures, including neurons and glia of the ENS [12–14]. A number of studies have demonstrated the presence of ENPCs within the fetal and postnatal ENS of rodents and humans [15–23] (Table 31.1). These resident endogenous

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Table 31.1 Properties of different stem/progenitor cells to treat Hirschsprung disease

	Adult stem cells	Pluripotent stem cells (PSCs)	
	Endogenous ENPCs	ES cells	iPS cells
Autologous cell source	Yes [15, 20, 23, 26, 29, 32, 35]	No [40]	Yes [41, 75, 76]
Proliferation ability	Limited [15, 59, 77]	Unlimited [40, 78]	Unlimited [41]
Neuronal differentiation in vitro	Yes: multiple subtypes [15, 20, 23, 29, 30, 32, 35]	Yes: multiple subtypes [45]	Yes: multiple subtypes [45, 46, 73]
Functioning neurons following transplantation in vivo	Yes; action potentials, fEPSPs, and calcium transients [23, 31, 32]	ND	ND
Functional integration to host neurons	Yes [31, 32]	ND	ND
Restoration of GI function of mouse with enteric neuropathies in vivo	Yes (restored colonic dysmotility of $nNOS^{-/-}$ mice) [30]	ND	ND
Rescue of mortality in animal model of HSCR	ND	Yes [45]	ND
Long-term survival and safety	Yes (~24 months with no tumor formation) [23, 32]	No (<3 months) [45]	ND (<3 months) [45]

Abbreviations: *ENPCs* enteric neural progenitor cells, *ES* embryonic stem (cells), *fEPSPs* fast excitatory postsynaptic potentials, *GI* gastrointestinal, *HSCR* Hirschsprung disease, *nNOS* neuronal nitric oxide synthase, *iPS* induced pluripotent stem (cells), *ND* not determined, *PSCs* pluripotent stem cells

ENS-derived ENPCs can be isolated, expanded in culture, and transplanted into the colon of postnatal mice in vivo [23–31]. Such cells successfully engrafted, survived for up to 24 months within the wall of recipient gut [32], migrated extensively, and formed enteric ganglion-like clusters containing glial cells and neurons, expressing some enteric neuron subtype markers, including nitric oxide synthase (NOS), choline acetyltransferase (ChAT), calbindin, and calretinin [23, 30, 31]. Importantly, those graft-derived neurons fired action potentials [23], integrated into the enteric neuronal circuitry [31, 32], and partially restored intestinal dysmotility in mice with enteric neuropathy [30] (Table 31.1). Those endogenous ENS-derived ENPCs have also been identified in postnatal human gut [20, 33–38], including ganglionated gut of human patients with HSCR [35, 37, 39]. When transplanted into the aganglionic segment of mouse or human HSCR, they colonized the gut and generated neuronal phenotypes [35, 37, 39]. These studies have highlighted tremendous advances in regenerative medicine for enteric neuropathies by identifying a source of tissue to restore the ENS and confirming the feasibility of autologous transplantation. As a next step, we need to determine whether the transplanted ENPCs are able to mitigate the gut motility defects observed in HSCR. This is an essential step to move this therapy to the clinical arena. It is still unclear if aganglionic-recipient gut exhibits functional rescue following cell transplantation in mouse models in vivo [29, 36]. Previous studies suggest that the transplanted ENPCs might have limited capacity to migrate, differentiate, and proliferate in the aganglionic gut [15, 21, 25, 29, 37] (Table 31.1).

31.2.2 Pluripotent Stem Cell (PSC)-Derived ENPCs

Pluripotent stem cells (PSCs) offer an exciting alternative to endogenous ENS-derived ENPCs for the treatment of enteric neuropathies because of their unique and powerful characteristics, near limitless self-renewal capacity, and the ability to give rise to any cell types [40, 41], including the ENS [42–46]. Embryonic stem (ES) cells derived from the inner cell mass of the blastocyst are pluripotent and capable of giving rise to all cell types in the body [47]. Their initial discovery [48, 49] and subsequent isolation from human embryos [40] led to significant interest for their use in regenerative medicine, especially given their potential to generate "unlimited" quantities of cells for replacement therapies. The generation of induced pluripotent stem (iPS) cells has been achieved by the reprogramming of mouse embryonic or adult fibroblasts back to a pluripotent state by introducing four transcriptional factors – Oct4, Sox2, Klf4, and c-Myc [41]. Successful reprogramming of differentiated human somatic cells into a pluripotent state raised the possibility of creating patient-derived stem cells [50], which would bypass both immunological problems and bioethical issues associated with hES cells. Recently developed protocol showed that pluripotent stem cells (PSCs) (i.e., ES cells and iPS cells) can be converted into neural crest cells [45, 46, 51–53]. Very recent seminal work by Fattahi et al. [45] demonstrated that ENPCs can be derived from human pluripotent stem cells (PSC-derived ENPCs) via induction to neural crest cells and selection of "enteric" lineage. They have been shown to give rise to functioning enteric neurons integrated into neuromuscular circuitry with expression of wide range of neurochemical subtypes in vitro. Following transplantation into colon of HSCR model mice in vivo, PSC-derived ENPCs displayed extensive migration to colonize whole segment of aganglionic colon and rescued the phenotype as well as improved mortality of mice with HSCR [45]. This work provides

significant validation for the use of human PSCs for the treatment of HSCR. However, it remains unclear how transplanted cells were able to elicit the rescue [45]. Overall, studies, such as the above, suggest that the ideal cell type for replacement therapies is likely to be a neural crest cell phenotype, and deriving them from PSCs may have the advantage of generating adequate cell numbers. However, much work is needed to investigate the function and safety aspects since unlimited cell proliferation may lead to a tumor formation within the host tissue following transplantation.

31.3 Practical Challenges in Developing Cell Therapies

Although there has been much progress in the sourcing of cells with potential for cell replacement therapy for HSCR, a number of key challenges still need to be addressed before effective clinical application as discussed below.

31.3.1 HSCR as an Ideal Target Disease

HSCR is extensively used as a classic example to study the potential of cell-based therapy for enteric neuropathies. However, it is still unclear whether transplanted neural progenitor cells can colonize entire segment of aganglionic colon and replace the missing ENS in HSCR. It is also unknown whether the whole complex ENS circuitry needs to be replenished to restore the dysmotility of aganglionic colon of HSCR. Moreover, normal peristaltic movement requires not only neurons and glial cells but also interstitial cells of Cajal (ICCs), which are unlikely to be regenerated from transplanted ENPCs because of their different developmental origin [54]. However, a very recent study has demonstrated increased ICC network in mice with enteric neuropathy following neural crest-derived ENPC transplantation and a rescue of impaired colonic motility by non-cell-autonomous (indirect) mechanism [30], suggesting that complete restoration of ENS network might not be necessary to reinstate normal gut motility. Another recent evidence showed aging-related neuronal loss is not associated with functional failure [55], giving hope that restitution of a full normal ENS is perhaps not needed to treat HSCR by cell therapy.

31.3.2 Is Optimization of Donor Cells and/or Microenvironment of Recipient Gut Required?

The discrepancy between the capacity of donor ENPCs and the recipient gut environment could also become a barrier for cell therapy. Rectosigmoid aganglionosis is the most common type of HSCR, and the aganglionic segment in these patients is typically several centimeters in length. However, most of the studies using endogenous ENS-derived ENPCs to date showed longitudinal migration of these cells in the recipient colon was only a few millimeters [23, 25, 30]. These findings raised two possibilities: (1) donor ENPCs retain limited migratory capacity and/or (2) the microenvironment of recipient (aganglionic) colon may not be feasible to be colonized. It has been demonstrated that adult gut-derived neural crest stem cells have a lower capacity to proliferate and produce neurons in comparison to fetal cells [15, 21, 35]. During the normal development of the ENS, cell number and cell-cell contact are critical factors to complete the colonization of gut [56, 57], suggesting that limited capacity of cell proliferation could slow down their migration. We and others have previously reported cell engineering approaches that successfully enhance the capacity of proliferation and migration of ENPCs following transplantation into mouse colon in vivo [58, 59]. For the use of endogenous ENS-derived ENPCs in clinical application, further optimization might be required.

With regard to the microenvironment of recipient colon, it has been shown that aganglionic colon of patients with HSCR exhibits decreased expression of glial cell line-derived neurotrophic factor (GDNF), a critically important neurotrophic factor for normal development of the ENS [60, 61]. Moreover, a few studies have demonstrated that HSCR mouse models display bacterial dysbiosis, impaired mucosal defense, and increased enteroinvasion of *E. coli*, leading to HSCR-associated enterocolitis [62, 63]. Therefore, aganglionic-recipient gut environment may not be permissive for newly introduced ENPCs to survive, colonize, and differentiate into appropriate cell types. Although the recent outstanding report by Fattahi et al. has shown that PSC-derived ENPCs are able to colonize entire colon, including aganglionic segment of mice with HSCR for 4 weeks following transplantation and give rise to glial cells and neurons expressing markers of multiple neuronal subtypes [45], it still remains unclear if those cells are functionally integrated to neuromuscular circuitry to restore the motility of aganglionic colon. Preconditioning the recipient aganglionic colon with factors that will support the survival, migration, and differentiation of the transplanted ENPCs might be helpful to maximize the success of cell therapy.

31.3.3 What Is the Best Way to Deliver Donor Cells to the Gut?

The main objectives while choosing a cell delivery technique is that the approach should be (1) able to deliver a large number of cells, (2) minimally invasive, (3) capable of permitting

accurate targeting and migration of cells in the aganglionic gut region, and (4) effective in improving gut function. Several approaches of cell delivery have been attempted in laboratory animals. However, the size of the gut and its complex multilayered structure adds to the challenges of cell delivery to this organ. The seromuscular approach via laparotomy has been widely used for delivery since it allows accurate targeting and introduction of large numbers of cells or neurospheres by large volume injections [45, 58, 64]. One drawback of this technique is the significant leakage of transplanted cells through puncture holes such that the cells might not engraft in the aganglionic gut region, resulting in a random distribution and poor reproducibility. Recent attempts have been made to overcome these drawbacks by incorporation of cells into biomaterials such as hydrogels, which polymerize in situ and enhance retention. For future clinical setting, ultrasound guided-laparoscopic or endoscopic injection might provide better precision and targeting into specific layers of interest in the gut.

31.3.4 Long-Term Safety and Efficacy

It has been demonstrated that PSC-derived ENPCs possess outstanding potential for use in cell-based therapy for HSCR, partially due to their limitless proliferation ability [45]. However, this unique characteristic of PSC-derived cells could be a disadvantage for clinical application since they may form tumor following transplantation into patients. In addition, the use of genome-integrating virus during iPSCs generation may cause random but permanent integration of exogenous transgenes into the host genome that can produce insertional mutations or may alter differentiation potential [65]. Although the rather longer safety (<24 months) has been shown in endogenous ENS-derived ENPCs following transplantation in vivo, further and more careful verification will be required to determine their safety before their clinical application.

Two potentially autologous cells sources, endogenous ENS-derived ENPCs and PSC-derived ENCS, discussed in this chapter hold an advantage to circumvent immune rejection, a huge obstacle in transplantation medicine. However, the use of autologous cells may be problematic since cells derived from patients with HSCR might possess genetic mutations that caused HSCR, which may result in their insufficient function [45, 66]. It has very recently been shown that those disease-related cell-autonomous defects can be corrected using CRISPR-/Cas9-based gene-targeting techniques [45, 67]; however, further investigation will be required to determine if the colonic function can be restored by transplantation of those patient-derived ENPCs cells in vivo.

31.4 Key Steps of Cell Therapy to Treat Patients with HSCR

There are several key steps likely to be required to treat children with HSCR using autologous cell transplantation as shown in Fig. 31.1. Fashioning temporary stoma will be the first key step although patients suffering from rectosigmoid HSCR are generally treated without enterostomy as discussed in other chapter. This step will provide an opportunity for clinicians/researchers to obtain full thickness of ganglionated bowel tissue (Step 2a, Fig. 31.1) from which ENS-derived ENPCs can be isolated and expanded [22, 37] (Step 3, Fig. 31.1). In order to establish patient-derived iPSCs, the first step may not be necessary, since skin or blood sample from patients are generally used (Step 2b, Fig. 31.1). Establishment of iPSCs followed by induction to neural crest lineage and purification of enteric population is likely to take a few months [45, 46] (Step 2b', Fig. 31.1) although the recently optimized protocol for generating iPSCs achieved short reprogramming times of a few weeks [68, 69]. It is likely that manipulation of ENPCs to correct deficit of patient-derived ENPCs will be required prior to the transplantation as discussed above (Step 3, Fig. 31.1). Following transplantation of ENPCs into the aganglionic region of HSCR patients (Step 4, Fig. 31.1), several weeks or even months would be required for transplanted cells to proliferate, migrate, and differentiate into neurons that form functional connection to host ENS and smooth muscle (Step 5, Fig. 31.1). And final step will be an analysis to test if colonic function can be sufficiently restored.

31.5 Summary and Future Directions

Cell therapy for HSCR is an exciting and promising prospect. The ENS has many potential advantages that favor the success of transplantation therapies. These include accessibility to both source and deliver cells, as well as the possibility of minimizing immune rejection by obtaining donor neural progenitor cells from unaffected regions of the intestine or using iPSCs technology for autologous transplantation. The evidence to date suggests that cells with the potential of generating components of the ENS can be harvested, propagated in culture, have their biological properties manipulated, and ultimately be transplanted into diseased or dysmotile gut to replenish components of the ENS and rescue function or even mortality of HSCR mice. Those significant advances have resulted in increased awareness of the field and driving force to shift toward definitive cures using cell therapy for HSCR. As discussed in proposed key steps for clinical application, a number of significant hurdles still remain, and perhaps all need to be addressed. For future

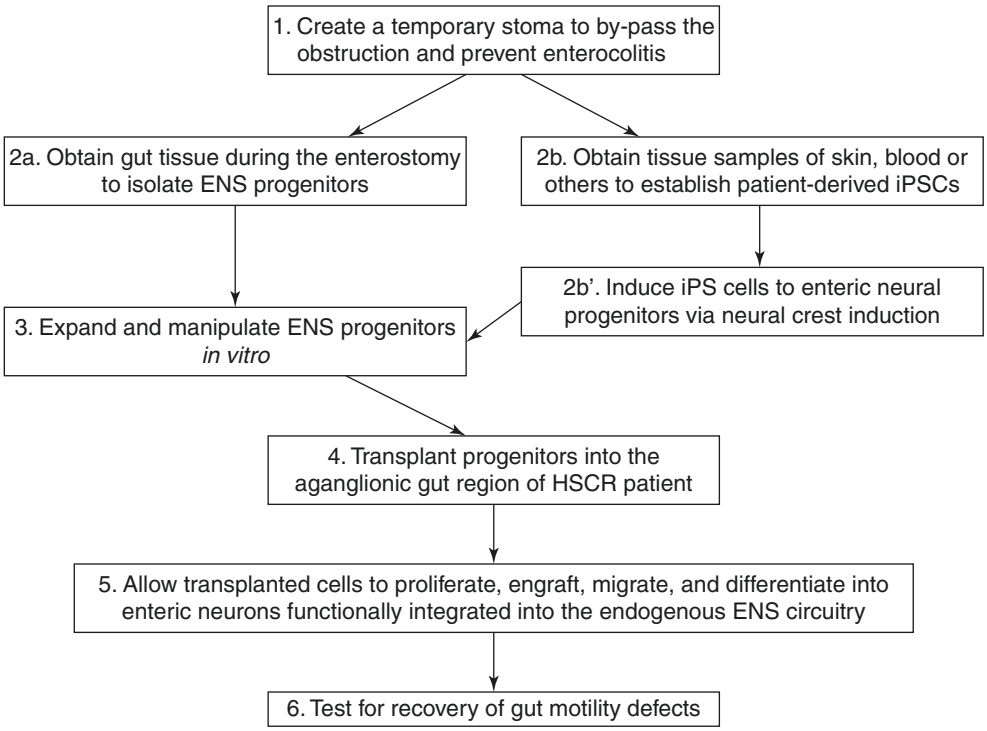

Fig. 31.1 Proposed steps for cell-based therapy to treat patients with Hirschsprung disease

directions to consider, the other aspect for the treatment of HSCR, generating intestinal organ from PSCs [70–72], can be beneficial, particularly for those with long-segment HSCR. Very recent reports have demonstrated that combination of PSC-derived ENPCs and human intestinal organoids successfully produce functioning intestinal tissues [73, 74] which might be able to replace the aganglionic intestine of long-segment HSCR.

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History of Allied Hirschsprung's Disease

32

Hiroshi Matsufuji

32.1 Introduction

Hirschsprung's disease shows transit disorder of intestinal content, delayed meconium excretion, abdominal distention, bilious vomiting, constipation, and intestinal dilatation (megacolon) at proximal side, resulting from aperistalsis and lack of the recto-anal reflex caused by aganglionosis of the distal segment. In the pediatric surgery field, the disease has been widely recognized, the condition has been elucidated, and the therapy has been developed. In these clinical and research settings, there is a disease group which has symptoms and laboratory findings similar to those of Hirschsprung's disease despite the presence of ganglion cells in the rectum. It has been called "allied Hirschsprung's disease" in Japan. However, the disease concept and diseases included in the group have been changed over time, and a consensus is not yet established among specialists.

32.2 History of the Concepts and Diseases Included Hirschsprung's Disease-Related Neuromuscular Disorders of the Intestine

The literatures review shows the concept also has been changed little by little over time. In 1958 Ravitch M published in *Annals of Surgery* precise report of cases as pseudo-Hirschsprung's disease [1]. And he summarized that Hirschsprung's disease may be mimicked in four groups of children with:

- Psychogenic constipation pseudo-Hirschsprung's disease. Unlike Hirschsprung's disease, symptoms do not appear at birth, encopresis is common, and the barium enema shows no narrow distal segment.
- Mental retardation and cerebral defects.
- Corrected imperforate anus on the basis of stenosis, imperfect innervation, or poor habit training.
- Cretinism-severe constipation and intestinal dilatation may be the presenting symptoms.

In 1965, a seminar on pseudo-Hirschsprung's disease and related disorders were held at the combined meeting of British Association of Pediatric Surgeons and the Surgical Section of the American Academy of Pediatrics in Edinburgh. Hirschsprung' s disease and allied disorders were listed as below (Table 32.1) [2].

Thereafter the clinical recognition and experiences of such diseases had been increased, and investigation and pathological examination methods had been advanced. A couple of new concepts of the disease have been reported.

In 1971 Meier-Ruge reported unknown pathogenesis-associated lower intestinal obstruction [3]. He described the intestinal neuronal dysplasia (IND) and modified the criteria for definition over the years. The disease has type A and type B. Type A is very rare, accounting for about 5% of IND, and presents as bowel obstruction, diarrhea, bloody stool, etc. during neonatal period. Reduction in intestinal sympathetic nervous system innervation is observed. As type B may account for 95% of IND, blockage of lower gastrointestinal tract is similar to that Hirschsprung's disease. It is still controversial whether the pathological finding is a congenial change, or secondary one related to growth process, or constipation.

In 1976 five newborn girls with megacystis-microcolon-intestinal hypoperistalsis syndrome were reported [4]. It is a serious disease which presents as bowel obstruction-like symptoms in neonatal period and later, resulting in intestinal failure, which is accompanied by megacystis and microcolon. Many of the cases require gastrointestinal decompression through gastric fistula or intestinal fistula during neonatal period. In pathological examination, abnormality is not observed in the intestinal nerve plexus.

PremPuri has focused its research interest into delineating variant Hirschsprung's disease based on specific histochemical, immunohistochemical, silver staining, and electron

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Table 32.1 Hirschsprung's disease and allied disorders

With abnormality of ganglion cells	Without abnormality of ganglion cells	
Hirschsprung's disease • Congenital megacolon • Congenital aganglionosis Chagas disease • Acquired megacolon • Aperistalsis Hypoganglionosis Immaturity of ganglion cells	Aetiology obscure	Clear aetiology
	Idiopathic megacolon • Functional megacolon • Psychologenic megacolon • Megarectum • Colonic inertia • Chronic constipation • Pseudo-Hirschsprung's disease • Segmental dilation of the colon • Achalasia of distal rectal segment	Symptomatic megacolon • Secondary megacolon (anal stricture, myxedema, cerebral atrophy)

microscopic studies in 1977 [5]. Between 1981 and 1996, he and colleagues had investigated full-thickness rectal biopsy or resected surgical specimens from 66 patients with clinical symptoms suggesting Hirschsprung's disease were examined. These had included intestinal neuronal dysplasia, hypoganglionosis, immature ganglia, absence of argyrophil plexus, internal sphincter achalasia, and smooth muscle disorders [4].

Variants of Hirschsprung's disease include:

- Intestinal neuronal dysplasia
- Intestinal ganglioneuromatosis
- Isolated hypoganglionosis
- Immature ganglia
- Absence of the argyrophil plexus
- Internal anal sphincter achalasia
- Congenital smooth muscle cell disorders such as megacystis-microcolon-intestinal hypoperistalsis syndrome.

Recent literatures on the Hirschsprung's and allied disorders have been reviewed, and the new concepts of allied disorders were published. It contains intestinal neuronal malformation (IND), neurocristopathies and particular association with Hirschsprung's disease, megacystis-microcolon-intestinal-hypoperistalsis syndrome, degenerative hollow visceral myopathy mimicking Hirschsprung's disease, adynamic bowel syndrome, anal sphincter achalasia, and ultrashort Hirschsprung's disease [5].

32.2.1 Past National Surveys in Japan

In Japan, the term of aganglionosis-related disease was used in "Neonate Surgery" in 1978, and in 1988 a survey report of allied Hirschsprung's diseases was released in *Journal of the Japanese Society of Pediatric Surgeons* (Akihiro Toyosaka). He defended the dieses on histopathological findings.

1. Abnormal findings of ganglion cells:
   (a) Hypoganglionosis
   (b) Oligoganglionosis
   (c) Hypogenesis of ganglia
   (d) Immaturity of ganglia
   (e) Neuronal intestinal dysplasia
2. No abnormal ganglion cells:
   (a) CIIPS
   (b) MMIHS

In 1993, a national survey was conducted by allied Hirschsprung's disease group research (Eizo Okamoto). Questionnaires were sent to the councilors of the Japanese Society of Pediatric Surgeons requesting data on pseudo-Hirschsprung's disease. Two definitions of pseudo-Hirschsprung's disease were given: (1) congenital, chronic, nonmechanical obstruction of the intestine and (2) the presence of intramural ganglion cells in the terminal rectum. A total of 93 replies were received, reporting 148 cases of pseudo-Hirschsprung's disease of which 77 were abnormal in the intramural ganglia and 42 were normal and 29 were unknown. In the abnormal group of the intramural ganglia, there were immaturity of ganglia or oligoganglionosis (54 cases), neuronal intestinal dysplasia (15 cases), and segmental anomaly (8 cases).

In the normal group of myenteric plexus, 22 were chronic idiopathic intestinal pseudo-obstruction syndrome (CIIPS), 12 cases were suspected CIIPS, and 8 cases of MMIHS.

The most of oligoganglionosis (or hypoganglionosis) or immaturity of ganglia showed negative rectoanal reflex and normal Ach-E activity, while most of the normal group of intramural ganglia revealed positive rectoanal reflex and normal Ach-E activity. The prognosis of oligoganglionosis (or hypoganglionosis), CIIPS, and MMIHS were very poor.

32.3 Recent Nationwide Survey for Allied Hirschsprung's Diseases in Japan

Development of this clinical practice guideline for allied Hirschsprung's diseases was triggered by a nationwide survey in the project of "Current situation survey for allied

Hirschsprung's diseases and development of guideline for the diagnostic criteria" by the Health and Labor Science Research in 2011 fiscal year [6]. Disease concept, classification, diagnostic criteria, and classification of severity were determined by "Comprehensive research for rare intractable gastrointestinal diseases from childhood."

32.3.1 Concept of Allied Hirschsprung's Disease

Allied Hirschsprung's diseases have been proposed to be the concept of the functional obstruction of the intestine with the presence of ganglion cells in the terminal rectum.

32.3.2 Definition of Allied Hirschsprung's Disease

Allied Hirschsprung's disease is a disease group which causes symptoms and signs similar to those of Hirschsprung's disease, such as bowel obstruction conditions, intestinal dilatation, and chronic constipation, despite the presence of ganglion cells in the rectum.

32.3.3 Classification of Allied Hirschsprung's Disease

The following seven diseases are defined as allied Hirschsprung's disease, which are classified based on the pathological findings of intestinal nerves from HE or Ach staining of intestinal tract or rectal mucosa samples collected at surgery or biopsy.

1. Diseases with abnormality in -intestinal ganglion cells:
(a) Immaturity of ganglia
(b) Isolated hypoganglionosis
(c) Intestinal neuronal dysplasia (IND)
2. Diseases without abnormality in intestinal ganglion cells (HE or AChE staining)
(d) Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS)
(e) Segmental dilatation of intestine
(f) Internal anal sphincter achalasia (IASA)
(g) Chronic idiopathic intestinal pseudo-obstruction (CIIP)

32.3.4 Epidemiological Characteristics of Allied Hirschsprung's Diseases

In total, 355 cases were collected. They included 28 immaturity of ganglia, 130 hypoganglionosis (121 congenital, 9 acquired), 18 intestinal neuronal dysplasia, 33 MMIHS, 43 SD, 3 IASA, and 100 CIIP [7]. Of the 95 institutes, 69 (72.6%) had their own criteria for allied Hirschsprung's diseases. Criteria were based on clinical symptoms and signs and conventional pathological examinations. Prognosis was poor in congenital hypoganglionosis, MMIHS, and CIIP, while the others showed good survival rates [8]. The table below shows the numbers of cases of allied Hirschsprung's diseases and survivals at major pediatric medical institutions for 10 years in Japan, which were summarized in the survey of "Current situation survey for Allied Hirschsprung's diseases." (Table 32.2)

Table 32.2 Epidemiological characteristics of allied Hirschsprung's diseases

Allied Hirschsprung's disease	Number of cases for primary survey	Number of cases for secondary survey	Number of definitive cases	Survival rate
1. Abnormal ganglion cell group				
(a) Immaturity of ganglia	19	28	28	100%
(b) Isolated hypoganglionosis	114	90	70	78%
(c) Intestinal neuronal dysplasia	17	11	11	100%
2. Normal ganglion cell group				
(d) Megacystis-microcolon-intestinal hypoperistalsis syndrome	29	19	10	53%
(e) Segmental dilatation of intestine	35	28	27	96%
(f) Internal anal sphincter achalasia	6	2	2	100%
(g) Chronic idiopathic intestinal pseudo obstruction	94	56	56	89%

32.4 Summary

It has been known that there are some patient groups who have symptoms and laboratory findings similar to those of Hirschsprung's disease despite the presence of ganglion cells in the rectum. It has been called pseudo-Hirschsprung's disease, allied disorders of Hirschsprung's disease or allied Hirschsprung's disease, and so on. However, consensus is not yet established and changing among specialists; a nationwide study has been conducted to investigate current status in Japan. In this chapter the history of the disease concept and diseases included have been reviewed.

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Classification and Pathology of Allied Hirschsprung's Disease

33

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33.1 Synonym

Variants of Hirschsprung's disease [1], Pseudo-Hirschsprung's disease [2].

33.2 Classification

"Allied disorders of Hirschsprung's disease (ADHD)" are a disease group that clinically resembles Hirschsprung's disease (HD), such as delayed passage of meconium and abdominal distention in the newborn period or severe chronic constipation in a young child, despite the presence of enteric ganglion cells [3]. HD is a defined entity, and the diagnosis is confirmed by histological and histochemical evaluation of rectal mucosal biopsies, which demonstrate the absence of ganglion cells in the submucosa and increased acetylcholinesterase (AchE) activity in the muscularis mucosae and lamina propria mucosae. However, ADHD are less well defined, and disease entities of ADHD have not been unified internationally [4, 5].

ADHD has been classified into two categories based on pathology by hematoxylin and eosin (HE) and AchE staining: (1) with abnormalities of ganglion cells, including immaturity of ganglia (IG), isolated hypoganglionosis (IHG), intestinal neuronal dysplasia (IND), diffuse intestinal ganglioneuromatosis, and absence of argyrophil plexus, and (2) without abnormalities of ganglion cells, including megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS), segmental dilatation of the intestine (SD), internal anal sphincter achalasia (IASA), and chronic idiopathic intestinal pseudo-obstruction (CIIP) [4–6] (Table 33.1). Current diagnostic algorithm for ADHD is shown in Fig. 33.1 [4, 7].

Chronic idiopathic intestinal pseudo-obstruction (CIIP) is a bowel disorder that shows recurrent or persistent functional intestinal obstruction with normal histology by conventional staining of HE and AchE. Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) has been considered to be the severe form of CIIP. However, MMIHS can be distinguished from CIIP by clinical characteristics [5, 8]. MMIHS and segmental dilatation of the intestine are also present with normal histology of intestinal ganglia and normal AchE activity.

33.3 Pathological Examination

33.3.1 Rectal Mucosal Biopsy (RMB)

RMB provides a larger and deeper biopsy than standard endoscopic forceps biopsies which are usually inadequate to obtain sufficient submucosa for the diagnosis. It is important that the biopsy is not taken too close to the dentate line because a normal zone of submucosal hypoganglionosis

Table 33.1 Classification for allied disorders of Hirschsprung's disease (modified Taguchi et al. [5])

(1) Abnormal ganglia (abnormal histology in hematoxylin and eosin or acetylcholinesterase staining)
• Immaturity of ganglia (or immature ganglionosis)
• Isolated hypoganglionosis (congenital, acquired)
• Intestinal neuronal dysplasia
• Diffuse intestinal ganglioneuromatosis[a]
• Absence of argyrophil plexus[a]
(2) Normal ganglia (normal histology in hematoxylin and eosin or acetylcholinesterase staining)
• Megacystis-microcolon-intestinal hypoperistalsis syndrome
• Segmental dilatation of the intestine
• Internal anal sphincter achalasia
• Chronic idiopathic intestinal pseudo-obstruction

[a]Included in the review by Friedmacher and Puri [4]

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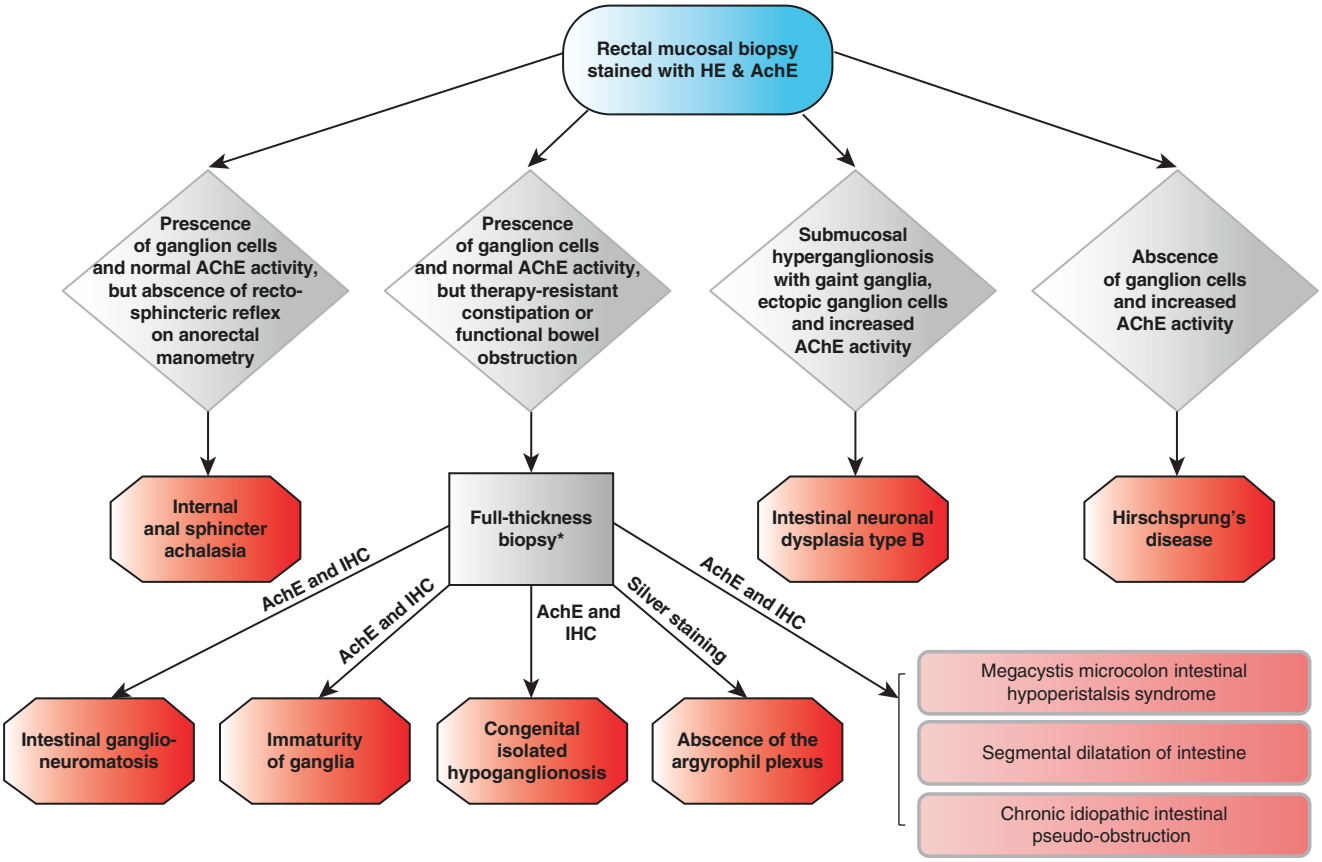

Fig. 33.1 Diagnostic algorithm for Allied disorders of Hirschspurung's disease by Friedmacher et al. with modification. *AchE* acetylcholinesterase staining, *IHC* immunohistochemistry. *Full-thickness biopsy from three locations; (1) at artificial anus that is enough oral side from narrow segment (caliber change), (2) terminal ileum, and (3) sigmoid colon

extends for approximately 10–25 mm above this point, increasing from 10 mm in neonates to 25 mm in 3-year-olds and above. Since accurate positioning of the RMB device at appropriate distance above the dentate line is sometimes difficult, some laboratories recommend that biopsies are obtained routinely from three separate levels (e.g., 1, 2, and 3 cm superior to the pectinate line).The primary goal of RMB is to exclude or confirm a diagnosis of HD. The frozen sections stained with HE plus AchE enzyme histochemistry and HE-stained paraffin-embedded section should be used as the standard techniques for the diagnosis of HD in rectal biopsies from children. The diagnostic utility of very few immunohistochemical markers has been tested in RMB. Calretinin is present normally in the cytoplasm and nerve processes of a subset of enteric ganglion cells. In the aganglionic segment of HD, calretinin immunoreactivity in muscularis mucosae and superficial submucosa is lost [9].

33.3.2 Full-Thickness Biopsy

When therapy-resistant constipation or functional bowel obstruction is continuously present, in spite of the fact that the presence of ganglion cells and normal AchE activity is confirmed by RMB, full-thickness rectal biopsy is required for differential diagnosis (Fig. 33.1). It is recommended to take enough size of intestinal specimen with 10 mm of longitudinal length and 5 mm of short axis. Immunohistochemistry is a very helpful and good diagnostic adjunct to be replaced for enzyme histochemistry to delineating the immature neurons (BCL2), the size of the enteric ganglion cell and neuromuscular innervation (S-100 protein, synaptophysin, and CD56, PGP9.5), and the intestinal cells of Cajal (c-kit) and myopathy (SMA) [5, 10]. Immunolocalization of the RNA-binding proteins, HuC/HuD, has been advocated as an excellent method for ganglion cell quantitation because HuC/HuD appears to be expressed in the cell body of virtually every mature and immature enteric ganglion cell [11]. The criteria to identify ganglion cells by Swaminathan et al. are as follows: an area of dark brown perikaryal staining in a cell that contains a nucleus and the granular stain must cover the nucleus or encircle at least 50% of circumference of the nucleus. If there was any ambiguity about the presence of a nucleus, the cell was not included [12]. In the evaluation of the size of the myenteric plexus by CD56 immunohistochemical staining, the CD56-

positive area between the circular and longitudinal layer of the muscularis externa is defined as the myenteric plexus [7]. In clinical practice, ADHD often develop a neonatal ileus and require an urgent surgery as is the case with intestinal atresia or HD. In such cases including isolated hypoganglionosis and immaturity of ganglia, intraoperative full-thickness biopsy is indispensable for diagnosis. Full-thickness biopsy is desirable to be taken from the three locations: (1) at the artificial anus that has enough oral side from a narrow segment (caliber change), (2) terminal ileum, and (3) sigmoid colon (Fig. 33.2). Immunohistochemical stainings for HuC/HuD and Sox10 are useful to evaluate the size and density of enteric ganglion cells and to identify enteric glia cells, respectively [7, 12, 13]. Immunohistochemical staining for CD56 is useful to evaluate the size of the myenteric plexus [7].A prerequisite is an understanding of the normal neuronal density, which varies depending on the following: (1) age, with an inverse relation between ganglion cells/plexus and age; (2) region of the examined bowel, fewer myenteric ganglion cells in the small intestine than the colon; (3) degree of intestinal dilatation, especially when the specimen is taken transversely along the long axis of the bowel; (4) type of biopsy and preparation (tissue sections vs whole mount preparation); and (5) mode of staining (marker). Hence, the diagnosis of quantitative abnormalities such as hypoganglionosis or hyperganglionosis in the myenteric plexus can be difficult, and a consensus in the detailed diagnostic criteria still remains to be found. Pathology of ADHD with abnormalities of ganglion cells is briefly described in the next.

33.4 Immaturity of Ganglia (IG)

The diagnosis of IG can be made from suction rectal biopsy. The immature ganglion cells appear very small and have a high nuclear-cytoplasmic ratio. The nucleolus is inconspicuous. It is often not possible to distinguish between these small ganglion cells and the enteric glial cells by HE morphology or

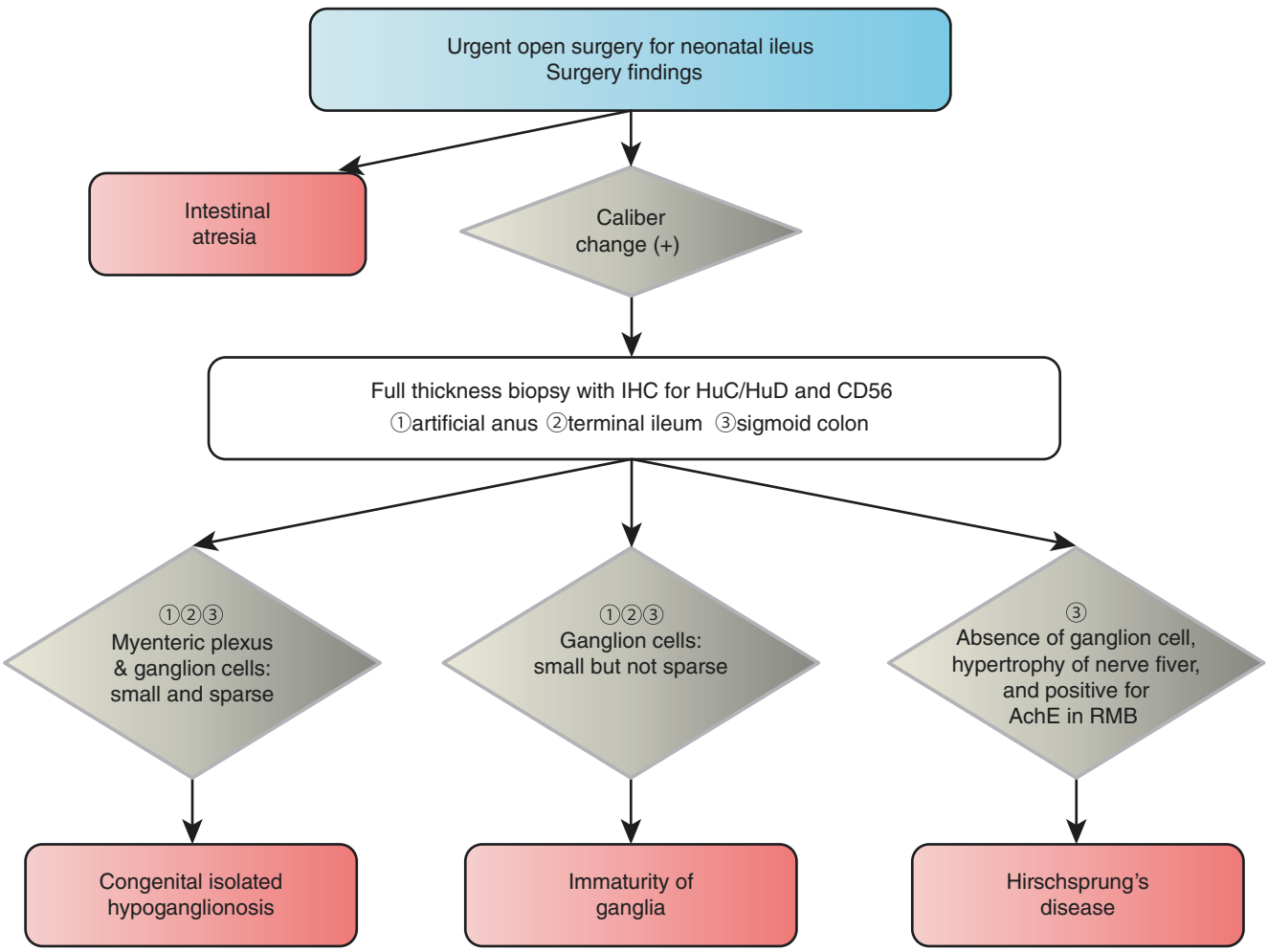

Fig. 33.2 Diagnostic algorithm for the differential diagnosis in urgent surgery for neonatal ileus. *IHC* immunohistochemistry, *AchE* acetylcholinesterase staining, *RMB* rectal mucosal biopsy

AchE histochemistry. HuC/HuD immunohistochemistry is helpful to identify immature small ganglion cells [12]. The density of ganglion cells is within normal range or may be highly cellular (Fig. 33.3). It has been demonstrated that this immaturity is a physiological, age-dependent phenomenon and maturation of ganglia strongly correlates with the age of the patient [3]. At the time of stoma closure, maturation of ganglion cells should be confirmed histologically.

33.5 Congenital Isolated Hypoganglionosis (IHG)

A full-thickness biopsy is required for the definitive diagnosis of isolated hypoganglionosis. To differentiate congenital IHG from HD accurately, full-thickness biopsy should be taken from the three locations (Fig.33.2). The myenteric plexus and ganglion cells are small and sparse (Fig. 33.4). AchE activity in lamina propria is absent or low and hypertrophy of the muscularis mucosae and circular muscle is also seen [4]. However, no consensus has been given on the detailed diagnostic criteria.

Meier-Ruge et al. found significant histological differences between resected bowel specimens from patients with congenital IHG and normal bowel tissue using AchE staining. They showed a 42% reduction in the number of ganglion cells in the plexus area and a 55% decrease of the ganglion cell number per mm length of the colon. The number and area of the myenteric plexus showed a decrease of 59% and a doubling of the plexus distances [14]. Although these observations form the basis for the histopathological diagnosis of congenital IHG, the evaluation of hypoganglionosis using coiled colon frozen section is technically difficult in practical diagnostic pathology. The consensus of diagnostic criteria using formalin-fixed paraffin-embedded specimen with immunohistochemistry is expected.

Yoshimaru et al. reported that neither HuC/HuD-positive cells nor CD56-positive myenteric plexus was

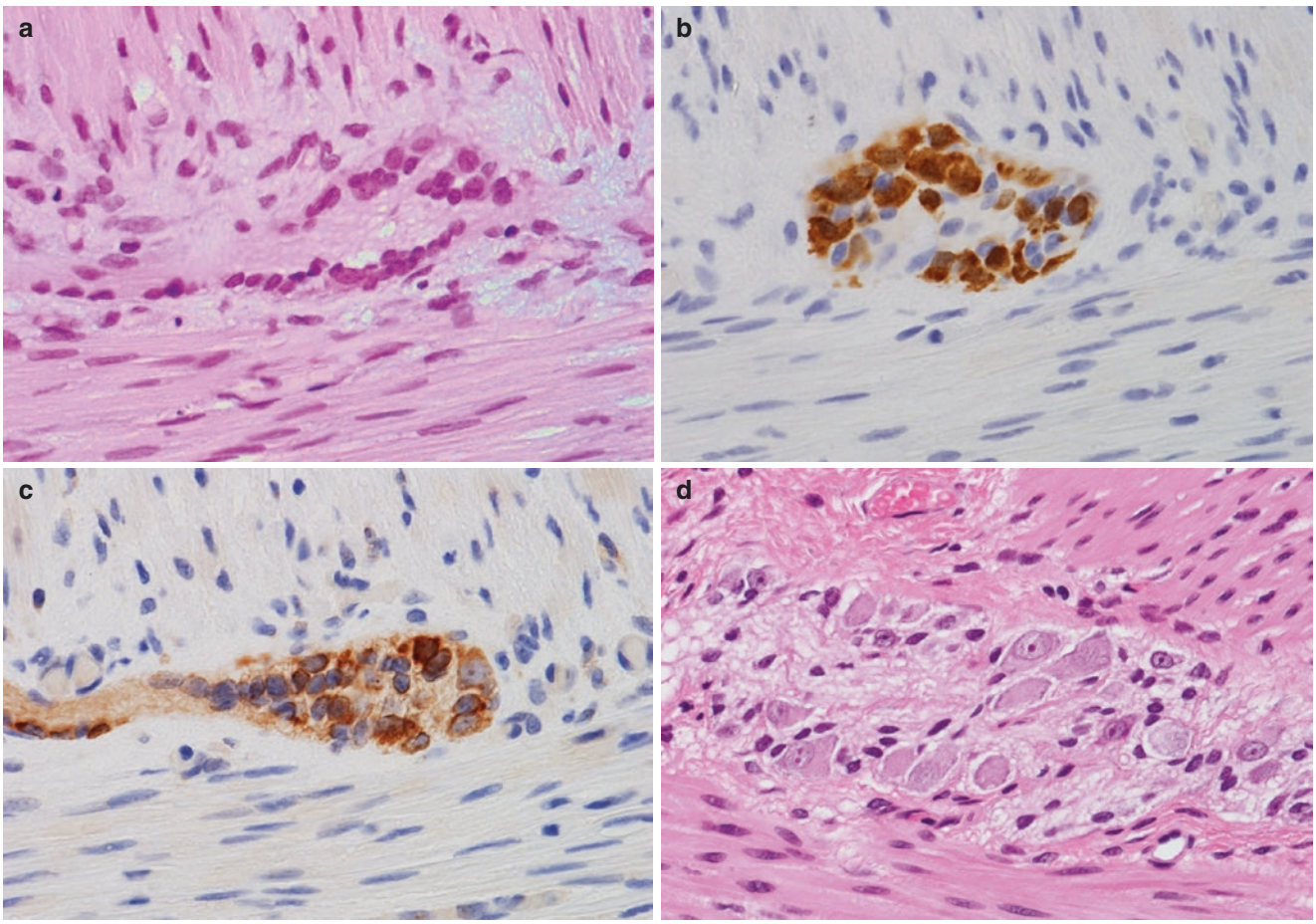

Fig. 33.3 Immaturity of ganglia. Myenteric plexus of the newborn include many immature ganglion cells with a high nuclear-cytoplasmic ratio and inconspicuous nucleoli. These cells are positive for HuC/HuD and BCL2 (**a**: HE staining, **b**: immunostaining for HuC/HuD, **c**: immunostaining for BCL2). Re-biopsy from the same patient at the age of 18 months shows the myenteric plexus including mature ganglion cells with abundant cytoplasm and prominent nucleoli (**d**: HE staining)

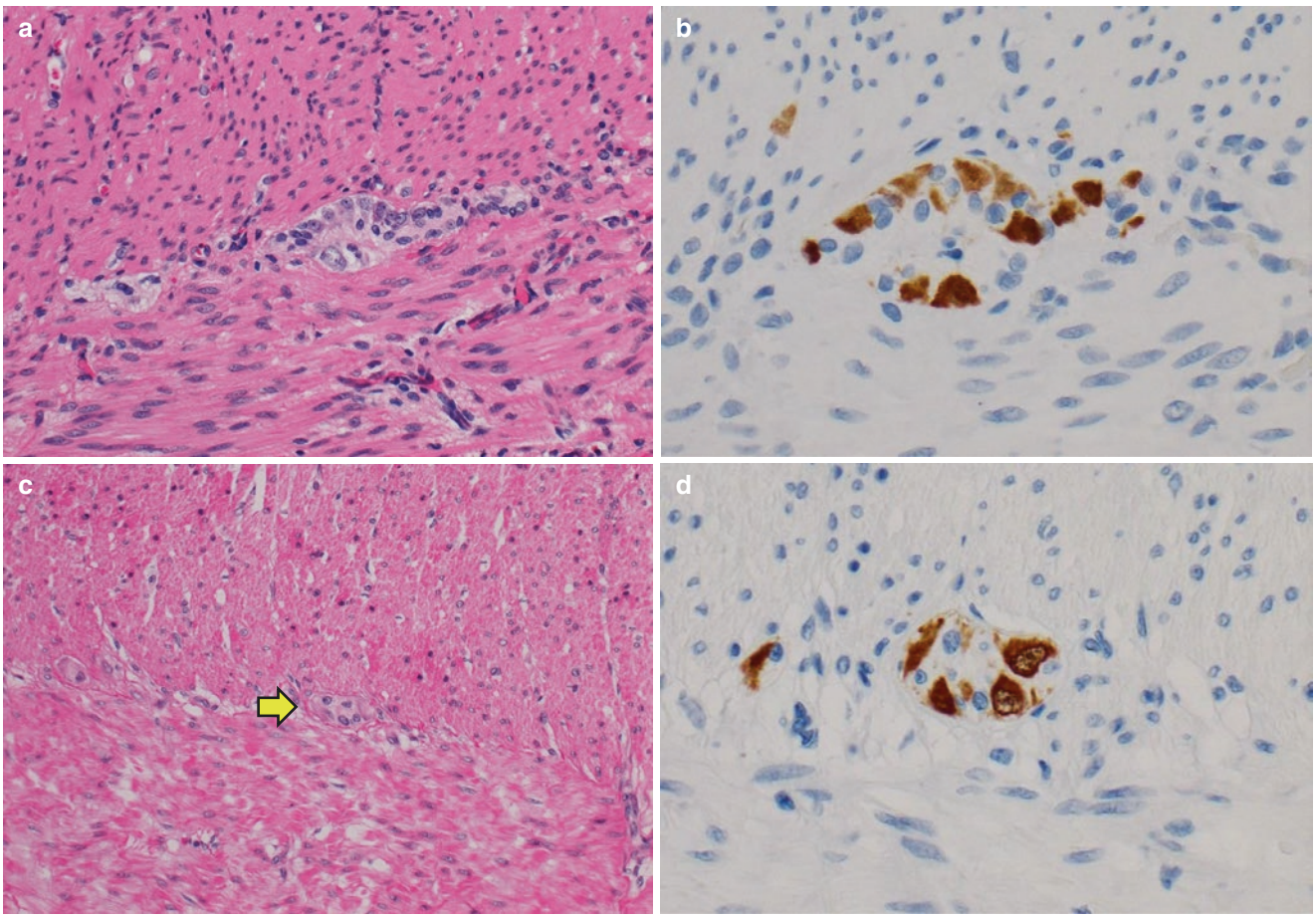

Fig. 33.4 Myenteric plexus of normal colon including mature ganglion cells (**a**: HE staining, **b**: immunostaining for HuC/HuD). In congenital isolated hypoganglionosis, myenteric plexus (arrow) are small and sparse with a few ganglion cells (**c**: HE staining, **d**: immunostaining for HuC/HuD)

present, but CD56-positive nerve bundles, which indicated an extrinsic innervation, were present in the aganglionic segment in HD. In the congenital IHG, a quantitative analysis revealed that the number of ganglion cells and the size of myenteric plexus were significantly smaller than that in the normoganglionic segment (NGS) of HD, while the number of ganglion cells was significantly smaller, but the size of the myenteric plexus was equivalent to NGS of HD in acquired IHG. They clearly showed that immunostaining using HuC/HuD and CD56 was useful to distinguish acquired IHG from congenital IHG; however, they could not achieve a quantitative cutoff value in comparison to the normal findings [7].

33.6 Intestinal Neuronal Dysplasia (IND)

IND has been classified into two clinical and histological distinct subtypes: IND type A and type B. IND type A is characterized by congenital aplasia, hypoplasia, or immaturity of the sympathetic innervation affecting the myenteric plexus as well as the submucosal arterial vessels and the mucosa. The biopsy specimen shows an ulcerative colitis or inflammatory changes and a total destruction of the muscularis mucosae. Aplasia of adrenergic innervation allows uninhibited overstimulation of cholinergic structures in the muscular layers, and dilatation of blood vessels leads to an increased mucosal permeability [3].

RMB with AchE enzyme histochemistry is the method of choice for the diagnosis of IND type B. RMB from IND type B shows hyperganglionosis, giant neural plexus (ganglia), and increased AchE activity in the lamina propria mucosae. However, the AchE activity in the lamina propria mucosae has been shown to be an age-dependent phenomenon that disappears on maturation of the submucosal plexus. Thus, the most commonly used diagnostic criteria is that more than 20% of 25 submucosal ganglia must be giant ganglia containing nine or more ganglion cells in patients older than 1 year, as before that age, giant ganglia may be misinterpreted due to the fact that immature ganglia often have an incomplete differentiation in ganglion cells. These criteria were developed with

15 μm-thick frozen section and AchE enzyme histochemistry. The correlation with counts on paraffin-embedded sections stained by HE or immunohistochemistry is unclear [4].

33.7 Diffuse Intestinal Ganglioneuromatosis

Intestinal ganglioneuromas are divided into three subgroups: (1) solitary polypoid ganglioneuromas that are typically asymptomatic tumors of the mucosa and submucosa with features similar to adenomas or juvenile polyps; (2) ganglioneuromatous polyposis characterized by multiple small mucosal polyps comprised of loose collections of mature ganglia, often resembling familial adenomatous polyposis and typically found in the colon and terminal ileum; and (3) diffuse ganglioneuromatosis (GNM). Diffuse intestinal GNM is characterized by diffuse proliferation of nerve fibers with significant hyperplasia of submucosal and myenteric ganglion cells causing thickening of the bowel wall. The patients with diffuse intestinal GNM present with severe chronic constipation and abdominal distention due to intestinal obstruction. This extremely rare condition is frequently associated with multiple endocrine neoplasia type 2B (MEN 2B), neurofibromatosis 1, or Cowden syndrome [15]. Mutation analysis in patients with MEN 2B further confirmed a de novo germline mutation of the *RET* proto-oncogene [16].

RMB or full-thickness biopsies of diffuse intestinal GNM show massive proliferation of submucosal and myenteric plexuses comprising thick nerve trunks with scattered mature ganglion cells, giant ganglia with often 15–40 ganglion cells, and a high AchE activity. Diffuse intestinal GNM appears to be largely confined to the colon and rectum, unlike neurofibromatosis, which occurs more commonly in the small intestine and stomach [17].

33.8 Absence of Argyrophil Plexus

In the normal myenteric plexus, there are two distinct subtypes of ganglion cells, i.e., argyrophil cells and argentaffin cells. Argyrophil cells coordinate the activation of argentaffin cells, which secrete specific neurotransmitters and ultimately cause contraction and relaxation of muscle fibers within the bowel wall. The lack of argyrophil cells in myenteric plexus, which is also known as absence of the argyrophil plexus, is a rare cause of severe constipation and functional bowel obstruction in infants and children. The absence of argyrophil cells and their neuronal processes can only be demonstrated using silver impregnation of full-thickness biopsies, while conventional HE staining, AchE histochemistry, and immunohistochemistry with several neuronal markers fail to show this abnormality [4].

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Allied Disorders of Hirschsprung's Disease: Nationwide Survey of Japan

34

Satoshi Ieiri and Tomoaki Taguchi

34.1 Introduction

Taguchi et al. [1] already reported the incidence and outcome of allied disorders of Hirschsprung's disease (ADHD) in Japan based on nationwide survey. After this nationwide survey, Japanese clinical practice guidelines for ADHD [2] had already been established. In this chapter, ADHD was explained based on this nationwide survey.

ADHD has been understood as the concept of intestinal hypoperistalsis, in spite of the presence of ganglion cells in the rectum [3–6]. In 1997, Puri proposed that "Variant Hirschsprung's disease" (VHD) is a more appropriate description and that VHD includes eight disorders: intestinal neuronal dysplasia (IND), intestinal ganglioneuromatosis, hypoganglionosis (Hg), immature ganglia, the absence of the argyrophil plexus, internal anal sphincter achalasia (IASA), smooth muscle cell abnormalities, perinuclear vacuolation, and megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS). The former four disorders are considered to be associated with abnormal ganglia, while the latter four disorders are considered to occur in patients with normal ganglia. We therefore decided to use the term ADHD, because Holschneider and Puri have used this term in their book *Hirschsprung's Disease and Allied Disorders* [5]. ADHD was defined as the disease presenting similar symptom of Hirschsprung's disease (HD) despite the existence of intestinal ganglion cells. The main point was that the various disease patterns were essentially determined by their underlying pathology.

In Japan, Okamoto and his colleague featured "ADHD" as the main theme and reported the results from nationwide survey at the 24th Congress of Japanese Association of Pediatric Surgeons in 1987 [7].

ADHD was classified into two categories based on the histological findings: those with abnormalities of ganglion cells and those without abnormalities of ganglion cells. We sympathize the Puri's classification based on pathological findings with or without abnormalities of ganglion cells. Two categories was shown in Table 34.1: abnormal ganglia, including immaturity of ganglia (IG), hypoganglionosis (congenital and acquired), and intestinal neural dysplasia (IND), and normal ganglia, including megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS), segmental dilatation of intestine (SD), internal anal sphincter achalasia (IASA), and chronic idiopathic intestinal pseudo-obstruction (CIIP).

In order to clarify the incidence and clinical feature of ADHD in Japan, Japanese Study Group of ADHD was organized by the support of the Ministry of Health and Welfare on 2011.

Table 34.1 Classification for allied disorders of Hirschsprung's disease in Japanese survey

(1) Abnormal ganglia (abnormal histology in hematoxyline eosin or acetylcholinesterase staining)
Immaturity of ganglia (or immature ganglionosis)
Hypoganglionosis (or oligoganglionosis)
Congenital hypoganglionosis (or hypogenesis, hypoplasia)
Acquired hypoganglionosis intestinal neuronal dysplasia
(2) Normal ganglia (normal histology in hematoxyline eosin or acetylcholinesterase staining)
Megacystis microcolon intestinal hypoperistalsis syndrome
Segmental dilatation of intestine
Internal anal sphincter achalasia
Chronic idiopathic intestinal pseudo-obstruction

Cited from "Table 2" of Taguchi T, Ieiri S, Miyoshi K, Kohashi K, Oda Y, Kubota A, Watanabe Y, Matsufuji H, Fu-kuzawa M, Tomomasa T (2017) The incidence and outcome of allied disorders of Hirschsprung's disease in Japan: Results from a nationwide survey. Asian J Surg. 2017;40(1):29–34. doi: https://doi.org/10.1016/j.asjsur.2015.04.004. Epub 2015 Jul 26

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Table 34.2 Number of patients in each disorder

	Definitive	Suspected	Total		Okamoto and Toyosaka [16]
Abnormal ganglia					
IG	22	6	28	(7.9)	26 (24.1)
HG	112	18	30	(36.6)	44 (40.8)
Congenital	104	17	121	(34.1)	
Acquired	8	1	9	(2.5)	
IND	8	10	18	(5.1)	5 (4.6)
Normal ganglia					
MMIHS	27	6	33	(9.3)	9 (8.3)
SD	33	10	43	(12.1)	NE
IASA	1	2	3	(0.8)	NE
CMP	84	16	100	(28.2)	24 (22.2)
Total	287	68	355	(100)	108 (100)

CUP chronic idiopathic intestinal pseudo-obstruction, *HG* hypoganglionosis, *IASA* internal anal sphincter acha-lasia, *IG* immaturity of ganglia, *IND* intestinal neuronal dysplasia, *MMIHS* megacystis microcolon intestinal hypoper-istalsis syndrome, *NE* not examined, *SD* segmentai dilatation

Cited from "Table 3" of Taguchi T, Ieiri S, Miyoshi K, Kohashi K, Oda Y, Kubota A, Watanabe Y, Matsufuji H, Fu-kuzawa M, Tomomasa T (2017) The incidence and outcome of allied disorders of Hirschsprung's disease in Japan: Results from a nationwide survey. Asian J Surg. 2017 Jan;40(1):29–34. doi: https://doi.org/10.1016/j.asjsur.2015.04.004. Epub 2015 Jul 26

34.2 Nationwide Survey

As a nationwide retrospective cohort study, supported by the Ministry of Health and Welfare, Japan, the preliminary questionnaires, requesting the number of cases of ADHD from January 2001 to December 2010, and the criteria of each institute were sent to the 161 major institutes of pediatric surgery or pediatric gastroenterology representing the core members of the Japanese Society of Pediatric Surgeons; the Japanese Society of Pediatric Nutrition, Gastroenterology, and Hepatology; and the Japanese Study Group of Pediatric Constipation. Therefore almost all institutes that are treating ADHD are considered covered. The number of patients, including the definite and suspected cases, based on the classification of ADHD in Japan (Table 34.1) and the survival rate and clinical outcome were asked. The criteria of each institute were asked to be answered as free descriptions. The criteria for definitive or suspected were dependent on each institute.

34.2.1 Overall Results

Replies were obtained from 157 of 161 institutes (98%). Out of 157 institutes, 95 (61%) had ADHD. In total, 355 cases, including 287 definite cases and 68 suspected cases, were collected between 2001 and 2010. More than half of the 95 institutes (53 institutes) had three cases or fewer. The mean number of cases per institute was 3.7 cases. There were 165 of 355 cases (47%) treated in university hospitals, 93 (26%) in children's hospitals, and 97 (27%) in general hospitals. ADHD included 28 IG [8], 130 HG (121 congenital, 9 acquired) [9, 10], and 18 IND [11] in abnormal ganglia and 33 MMIHS [12], 42 SD [13], 3 IASA [14], and 100 CIIP [15] in normal ganglia, and these numbers were compared with those of the previous study in Japan [16] (Table 34.2).

34.2.2 Diagnosis and Criteria

Of the 95 institutes who experienced ADHD, 69 (73%) had their own criteria. The percentages of institutes that had criteria for each disorder were between 28% and 83% (Table 34.3). More than 80% of institutes had criteria for congenital HG and CIIP, while only 30% institutes had criteria for acquired HG and IASA. Criteria of each disorder were based on clinical symptoms and signs, examinations including radiography findings, manometric study, and conventional pathological examinations including hematoxylin eosin (HE) and acetylcholinesterase (AchE). According to answers of the questionnaires, the major criteria listed in each disorder are as follows. IG: small ganglion cells, 37/46 (80%); number and distribution of ganglion cells are normal, 19/46 (41%); chronological improvement of clinical symptoms, 8/46 (17%); intestinal obstruction on neonatal onset, 6/46 (13%); normal AchE staining, 3/46 (7%); abdominal distention, 2/46 (4%); and microcolon, 2/46 (4%). Congenital HG: few ganglion cells, 41/55 (75%); few small ganglion cells, 14/55 (25%); intestinal obstruction on neonatal onset, 11/55 (20%); hypoplasia of plexus, 4/55 (7%); normal AchE staining, 4/55 (7%); negative rectosphincteric reflex, 4/55 (7%); and delayed meconium pass, 2/55 (4%). Acquired HG: ganglion cells decrease in number after some time, 6/19 (32%); few gan-

Table 34.3 The percentages of institutes that had criteria for each disorder

Abnormal ganglia		
IG	46/69	(67%)
HG		
Congenital HG	55/69	(80%)
Acquired HG	19/69	(28%)
IND	34/69	(49%)
Normal ganglia		
MMIHS	47/69	(68%)
SD	42/69	(61%)
IASA	21/69	(30%)
CIIP	57/69	(83%)

CIIP chronic idiopathic intestinal pseudo-obstruction, *HG* hypoganglionosis, *IASA* internal anal sphincter acha-lasia, *IG* immaturity of ganglia, *IND* intestinal neuronal dysplasia, *MMIHS* megacystis microcolon intestinal hypoper-istalsis syndrome, *SD* segmentai dilatation
Cited from "Table 2" of Taguchi T, Ieiri S, Miyoshi K, Kohashi K, Oda Y, Kubota A, Watanabe Y, Matsufuji H, Fu-kuzawa M, Tomomasa T (2017) The incidence and outcome of allied disorders of Hirschsprung's disease in Japan: Results from a nationwide survey. Asian J Surg. 2017 Jan;40(1):29–34. doi: https://doi.org/10.1016/j.asjsur.2015.04.004. Epub 2015 Jul 26

glion cells, 4/19 (21%); normal at birth and symptoms occur after some time, 2/19 (11%); no congenital factors, 2/19 (11%); chronic constipation and persistent bowel dilatation, 2/19 (11%); and normal AchE staining 1 (5%). IND: increased AchE positive fibers in the lamina propria, 17/34 (50%); ectopic ganglion cells, 14/34 (41%); giant ganglia (>5 ganglion cells per plexus), 13/34 (38%); severe constipation or rectal dysmotility, 9/34 (26%); hyperganglionosis, 6/34 (18%); and dilatation of bowel, 2/ 34 (6%). MMIHS: megacystis, 39/47 (83%); permanent severe symptoms of intestinal obstruction, 35/47 (74%); microcolon, 27/47 (57%); normal histology of intestinal neurons and muscles, 25/47 (53%); neonatal onset, 16/47 (34%); normal AchE staining, 5/47 (11%); and positive rectosphincteric reflex 4/47 (9%). SD: persistent segmental dilatation, 36/42 (86%); normal histology of intestinal ganglion cells, 24/42 (57%); no mechanical obstruction distal to dilatation, 13/42 (31%); signs of intestinal obstruction in radiography, 7/42 (17%); complete curability after resection of dilated bowel, 5/42 (12%); abrupt caliber change to the normal intestine, 3/42 (7%); thick or thin muscle layer, 2/42 (5%); and positive rectosphincteric reflex, 2/42 (5%). IASA: negative rectosphincteric reflex, 9/21 (43%); normal AchE staining, 9/21 (43%); severe constipation since birth, 7/21 (33%); and the absence of narrow segment, 4/21 (19%). CIIP: symptoms of intestinal obstruction without mechanical cause, 57/57 (100%); normal histology of intestinal ganglion cells, 46/57 (81%); abnormality of urinary tract, 13/57 (23%); dilatation of the intestine in radiography, 9/57 (16%); positive rectosphincteric reflex, 8/57 (14%); intermittent or recurrent symptoms, 6/57 (11%); and normal AchE staining, 6/57 (11%).

34.2.3 Survival Rate and Dietary Status

The survival rates of each entity for which the follow-up data were available are shown in Table 34.4. Three entities, congenital HG [9], MMIHS [12], and CIIP [15], showed poor survival rate, compared with those of the other five entities. These three entities required long-term nutritional support, including parenteral and enteral nutrition as shown in Table 34.5. In particular, outcome is extremely poor in MMIHS [12].

Table 34.4 Survival rate of ADHD

Abnormal ganglia	Survival rate	
IG	28/28	(100%)
HG		
Congenital HG	70/90	(78%)
Acquired HG	8/8	(100%)
IND	11/11	(100%)
Normal ganglia		
MMIHS	10/19	(53%)
SD	27/27	(100%)
IASA	3/3	(100%)
CIIP	50/56	(89%)

CUP chronic idiopathic intestinal pseudo-obstruction, *HG* hypoganglionosis, *IASA* internal anal sphincter acha-lasia, *IG* immaturity of ganglia, *IND* intestinal neuronal dysplasia, *MMIHS* megacystis microcolon intestinal hypoper-istalsis syndrome, *SD* segmentai dilatation
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Table 34.5 Dietary status of three poor entity

	Survival rate	Normal diet in survivors	Normal diet in all cases
Congenital HG	70/90 (78%)	42/69 (60%)	42/89 (48%)
CMP	50/56 (89%)	13/50 (26%)	13/56(23%)
MMIHS	10/19 (53%)	1/10 (10%)	1/19(5%)

CMP chronic idiopathic intestinal pseudo-obstruction, *HG* hypoganglionosis, *MMIHS* megacystis microcolon intestinal hypoperistalsis syndrome
Cited from "Table 6" of Taguchi T, Ieiri S, Miyoshi K, Kohashi K, Oda Y, Kubota A, Watanabe Y, Matsufuji H, Fu-kuzawa M, Tomomasa T (2017) The incidence and outcome of allied disorders of Hirschsprung's disease in Japan: Results from a nationwide survey. Asian J Surg. 2017 Jan;40(1):29–34. doi: https://doi.org/10.1016/j.asjsur.2015.04.004. Epub 2015 Jul 26

34.3 Summary

Almost all Japanese cases of ADHD for 10 years from 2001 to 2010 were collected by nationwide survey. Congenital HG and CIIP showed relatively high incidence, whereas acquired HG and IASA were extremely rare. Criteria of each institute were consisted with clinical signs, symptoms, and conventional histological examinations including AchE staining. For definitive pathological diagnosis of ADHD, immunohistochemical staining has been reported to be useful using neuronal and muscular markers, such as Bcl-2 for immature neurons; CD56 for the size of enteric ganglia; synaptophysin for neuromuscular innervation; S-100 protein for Schwann cells; c-kit for interstitial cells of Cajal; and smooth muscle actin for myopathy [17, 18].

Congenital HG, MMIHS, and CIIP showed poor survival rate [1]. Further collection of each case follow-up data and precise analysis of cases after establishing of Japanese clinical practice guidelines for ADHD [2] is required to obtain better treatment strategies and prognosis for ADHD patients.

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Genetic Aspect of Allied Disorders of Hirschsprung's Disease

35

Kosuke Kirino and Koichiro Yoshimaru

35.1 Classification of ADHD

Allied disorders of Hirschsprung's disease (ADHD) is a disease group which causes symptoms and signs similar to those of Hirschsprung's disease (HSCR), such as bowel obstruction conditions, intestinal dilatation, and chronic constipation, despite the presence of ganglion cells in the rectum [1]. In recent nationwide survey for ADHD in Japan, disease concept, classification, diagnostic criteria, and classification of severity were determined [1, 2]. The classification is based on the pathological findings of intestinal nerves from HE or acetylcholine esterase staining of intestinal tract or rectal mucosal samples (Table 35.1). Considering that normal gastrointestinal motility depends on coordinated action of the enteric nervous system (ENS), interstitial cells of Cajal (ICC), and smooth muscle cells (SMCs), ADHD can also be classified based on the cell types affected [3–5]. This concept can divide this disease group into three major entities: "neuropathies," "mesenchymopathies," and "myopathies," depending on the predominant involvement of enteric neurons, ICC, or smooth muscle cells (Table 35.2) [3–6].

35.2 Neuropathies

The ENS originates from enteric neural crest-derived cells (ENCCs) that undergo migration in the gut in about embryonic week 5 in humans and follows the vagal pathways progressing down the gut and reach the rectum by week 12 of fetal life [7, 8]. These ENCCs give rise to the majority of neurons and glial cells of the enteric ganglia and form the ENS [7, 8]. As they migrate, the ENCCs undergo key developmental processes, such as migration, proliferation, differentiation, and survival, to form a functional ENS. As a result, the ENCCs then form definable intramural ganglia and differentiate into at least 14 different classes of cells that undertake the functions of motility, sensory response, secretion, and the control of blood flow [7, 8]. The subject is very complex, and these mechanisms of ENS development are under the molecular control of numerous signaling pathways, transcription factors, neurotrophic factors, and extracellular matrix components [9]. It is possible that failure in these developmental processes then results in enteric neuropathies [7–9].

The most common form of enteric neuropathies is HSCR which is characterized by a lack of enteric neurons in the distal part of the gastrointestinal (GI) tract [7, 8]. A genetic bias of HSCR has been elucidated, and many genes and pathways have been identified as essential factors in the ENS development (see also Chap. 3) [7, 8]. In the context of exploration in genetics of HSCR, researchers have generated interest in creating genetic models in mice to help better understand of the ENS development [7–10].

Table 35.1 Classification of ADHD from nationwide survey in Japan [1]

1. Diseases with abnormality in intestinal ganglion cells
(a) Immaturity of ganglia
(b) Isolated hypoganglionosis
(c) Intestinal neuronal dysplasia, IND
2. Diseases without abnormality in intestinal ganglion cells
(d) Megacystis-microcolon-intestinal hypoperistalsis syndrome, MMIHS
(e) Segmental dilatation of the intestine
(f) Internal anal sphincter achalasia, IASA
(g) Chronic idiopathic intestinal pseudo-obstruction, CIIP

Table 35.2 Classification of ADHD based on cell types affected

• Neuropathies
• Mesenchymopathies (ICC abnormalities)
• Myopathies
• Others

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The RET-GDNF signaling pathway and the endothelin signaling pathway are two major pathways related to HSCR phenotype. Mice lacking *Ret*, *Gdnf*, *Ednrb*, or *Edn3* show aganglionosis [11–16]. Interestingly, dosage of these key genes affects the phenotype as mice heterozygous for *Gdnf* null allele and *Ednrb*$^{s/s}$ mice (homozygous for *Ednrb* hypomorphic allele) show hypoganglionosis [17, 18]. Genes such as *Hlx1* (H2.0-like homeobox), *Ntf3* (neurotrophin 3), and *Ntrk3* (neurotrophic tyrosine kinase, receptor, type 3, also known as *TrkC*) are also involved in the phenotypes of hypoganglionosis in mice [19, 20].

Pten (phosphatase and tensin homolog) homozygous conditional knockout mice have hyperganglionosis and are reported to develop intestinal pseudo-obstruction [21]. Another interesting gene *Tlx2* (T-cell leukemia, homeobox 2) has also been potentially related to functional obstructions in mice [22, 23]. Approximately half of these mice lacking *Tlx2* developed functional GI obstruction and cecal distension. Histological evaluation demonstrated significant increase of ganglion cells in the myenteric plexuses of the colon with a decrease in ganglion cell density in the distal small intestine reminiscent of those described in human IND [24].

In addition to all of these findings related to the number of ganglion cells, specification of neurotransmitter also affects the function of GI motility in mice [25]. Deletion of *Hand2* (heart and neural crest derivatives expressed 2) in enteric neural precursor cells resulted in lethal neurogenic pseudo-obstruction [25]. Histopathological findings showed complete loss of NOS and VIP and a significant decrease in the expression of choline acetyltransferase and calretinin, demonstrating a role for *Hand2* in neurotransmitter specification and/or expression [25]. Thus, the loss of specific neuronal cell types in the ENS might be critical for GI motility [6, 9].

Although genotype-phenotype correlation in ENS is substantially different between humans and mice [7, 10], these phenotypes of model mice suggest that congenital hypoganglionosis, IND (especially IND type B), and neuropathic types of chronic idiopathic intestinal pseudo-obstruction (CIIP) might be caused by genetic factors [3–6]. However, no mutation in these genes was found in patients with ADHD [3, 4, 6].

35.3 Mesenchymopathies (ICC Abnormalities)

ICC are interstitial cells found in the GI tract and originate mainly from KIT-positive mesenchymal mesodermal precursors [26, 27]. ICC serve as electrical pacemakers and generate spontaneous electrical slow waves in the GI tract [26, 27]. Electrical slow waves spread from ICC to SMCs, and the resulting depolarization initiates calcium ion entry and contraction [26, 27]. Slow waves organize gut contractions into phasic contractions that are the basis for peristalsis and segmentation [26, 27]. Alterations in the ICC network have been reported in adult patients with chronic intestinal pseudo-obstruction [3–5]. Electron microscopy or KIT immunolabeling combined with image analysis demonstrated a quantitative decrease in ICC along with structural abnormalities such as the loss of processes and damaged intracellular cytoskeleton and organelles [28, 29]. The evidence of significant changes in the ICC network further illustrates the critical role played by these non-neuronal cells in regulating gut motility [28, 29]. We cannot exclude the secondary phenotypes in ICC due to primary low GI function. However, ICC may play a role in congenital disorder such as CIIP.

35.4 Myopathies

Recently, the loss of SMC contraction has been found to underlie the development of one of the diseases in ADHD, megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS). MMIHS is a rare congenital disease of the visceral organs, mainly characterized by bladder distension and the presence of a microcolon [30]. This link was made from the identification of pathogenic variants in a SMC-related gene: actin, gamma 2, smooth muscle, and enteric (*ACTG2*) [30–33]. Four additional genes, myosin heavy chain 11 (*MYH11*) [34, 35], leiomodin 1 (*LMOD1*) [36], myosin light-chain kinase (*MYLK*) [37], and myosin light chain 9, regulatory (*MYL9*) [38] are also identified as pathogenic genes in MMIHS (Table 35.3). Variants in ACTG2 are implicated in the autosomal-dominant form of MMIHS [30–33], whereas homozygous variants in *MYH11*, *LMOD1*, *MYLK*, and *MYL9* cause a recessive form of t he disease [34–38].

These genes encode proteins associated with the smooth muscle contraction, supporting a myopathic basis for the disease [3, 4]. The *ACTG2* variants are also involved in some patients with CIIP [31–33], indicating that MMIHS and myopathic form of CIIP share the same disease entity and severity of the disease varies during affected individuals. In vitro study shows that ACTG2 variant proteins not only impair actin polymerization but also contribute to reduced cell contractility [39]. These findings bring new insights into the pathogenesis of enteric myopathies.

Table 35.3 Responsible genes for enteric myopathies

Gene	Location	OMIM	Phenotype	Inheritance
ACTG2	2p13.1	102545	MMIHS/ CIIP	Dominant, de novo, or inherited
MYH11	16p13.11	160745	MMIHS	Recessive
LMOD1	1q32.1	602715	MMIHS	Recessive
MYLK	3q21.1	600922	MMIHS	Recessive
MYL9	20q11.23	609905	MMIHS	Recessive

35.5 Future Perspectives

Although the pathology of ADHD requires further study before an effective nosology can be definitely proposed, combined clinical and histopathological studies should be encouraged in order to provide the basic framework for standardizing the histological evaluation of tissue obtained from patients with ADHD. The growing knowledge in genetics (especially in enteric myopathies) helps us understand the pathogenesis of ADHD and is fundamental for generating new therapeutic approaches.

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Immaturity of Ganglia

36

Satoshi Ieiri and Tomoaki Taguchi

36.1 Introduction

Ieiri et al. [1] already reported the clinical features in the diagnosis and treatment for immaturity of ganglia (IG) in Japan based on nationwide survey. In this chapter, IG was explained based on this nationwide survey.

Historically, Okamoto and his colleague featured "Allied Disorders of Hirschsprung's Disease (ADHD)" as the main theme and reported the results from nationwide survey at the 24th Congress of Japanese Association of Pediatric Surgeons in 1987 [2]. In these reports, IG was reported as the disease of normal number and extremely immaturity of ganglion cell in intestinal wall. Since then more detailed survey was performed by "Clinicopathological studies on the diagnosis, the treatment and the pathogenesis of pseudo-Hirschsprung's disease and related disorders" founded by Japan Society for the Promotion of Science from 1991 to 1993. In the reports of this study, IG was reported as follows: meconium ileus without mucoviscidosis, meconium disease-like findings on laparotomy, small and extremely immaturity in both nucleus and cell in ganglion cell of not only narrow small intestine but also enlarged small intestine, maturation of ganglion cells several months after ileostomy with recovering bowel function, and normal function with good prognosis. From another side, pathogenesis of meconium ileus without mucoviscidosis was based on meconium ileus without mucoviscidosis. "Immature ganglionosis" was proposed as the name for this disease group. In conclusion of this study, "immature ganglionosis" presented the pathological immaturity of fetal period under 5–6 months [3, 4].

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After these studies, Taguchi et al. [5] reported that the immature ganglion cells matured with time. So prognosis of this disease was so favorable; the comprehensive survey was not made after that. The assumed representative clinical features of the IG were as follows: (1) neonatal onset of ileus symptom, (2) microcolon–small colon findings in contrast enema, (3) negative anorectal reflex in manometry in neonatal period changing normal in infant period, (4) meconium disease-like finding in laparotomy, (5) lesion extending to the small intestine, and (6) bowel function recovering on time.

36.2 Nationwide Survey

A retrospective cohort study was performed as two-step nationwide survey. As the first step survey, preliminary questionnaires requesting the number of cases of all ADHD (IG, hypoganglionosis, internal anal sphincter achalasia (IASA), chronic idiopathic intestinal pseudo-obstruction (CIIP), segmental dilatation (SD) of the intestine, megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS), and intestinal neuronal dysplasia (IND)) seen from January 2001 to December 2010 and the criteria used at each institute to detect all number of ADHD patients were sent to 161 major institutes of pediatric surgery or pediatric gastroenterology, representing the core members of the Japanese Society of Pediatric Surgeons; the Japanese Society of Pediatric Nutrition, Gastroenterology, and Hepatology; and the Japanese Study Group of Pediatric Constipation.

As the results, specific independent pathophysiology of IG different from another ADHD was introduced from this survey. These included 28 IG (7.9%) patients. The second step survey was performed for 355 ADHD patients. Out of 28 case report forms sent as part of the second step survey, all 28 IG cases were subsequently collected. These 28 cases included "definitive" or "suspected." Thirteen of 28 cases were excluded because there were no histological evidence for IG at each institute. Finally, 15 cases of "definitive" IG

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were included in this article. Definitive 15 cases were diagnosed by pathological examination with hematoxylin-eosin (HE) staining by pathologist of each institute.

36.2.1 General Features

Male-female ratios were 9:6, the mean birth weights for patients with IG were 2473 g, and the mean gestational age was 36 weeks and 3 days. IG Patients with a positive family history was 4 case (26.7%), 2 in other twin baby and 2 in cousin. The incidence of associated anomalies was 1 (6.7%) case of mesenteric hernia. No chromosomal anomaly was recognized. No genetic examination was performed.

36.2.2 Imaging and Examination Findings

The onset of all 15 patients is neonatal period. For diagnosis, abdominal X-ray was performed in 100%. Abnormal intestinal distention was recognized in 13 cases (86.7%), niveau in 2 cases (13.3%), and free air in 2 cases (13.3%). Contrast enema was performed in 12 cases (80.0%). Microcolon was recognized in seven cases (58.3%) and a caliber change in three cases (25.0%). Anorectal manometry was performed in eight cases (53.3%). Positive anorectal reflex was recognized in four cases (50%), negative in two cases (25%), and atypical positive in two cases (25%) (Table 36.1).

Table 36.1 Imaging and examination findings

Abdominal X-P	
15 Cases (100%)	
Abnormal intestinal distenlion	13 (86.7%)
Nivean	2 (13.3%)
Free air	2 (13.3%)
Contrast enema	
12 Cases (80%)	
Microcolon	7 (58.3%)
Caliber change	3 (25%)
Normal	1 (8.3%)
Unknown	1 (8.3%)
Anorectal manometry	
8 Cases (53.3%)	
Anorectal reflex	
Positive	4 (50%)
Atypical positive	2(25%)
Negative	2 (25%)

Cited from "Table 3" of Ieiri S, Miyoshi K, Nagata K, Miyata J, Kohashi K, Oda Y, Taguchi T (2015) Current clinical features in diagnosis and treatment for immaturity of ganglia in Japan: analysis from 10-year nationwide survey. Pediatr Surg Int. 2015 Oct;31(10):949–54. doi: https://doi.org/10.1007/s00383-015-3774-0. Epub 2015 Aug 22

Table 36.2 Operative findings and surgical procedures

Laparotomy findings	
Abnormal distension on intestine	8 (61.5%)
Caliber change	8 (61.5%)
Microcolon	5 (38.5%)
Surgical procedure type	
Enterostomy	13 (86.7%)
Double barrel	11 (84.6%)
Bishop-koop	1 (7.7%)
Tube enterostomy	1 (7.7%)
Position	
Jejunum	2 (15.4%)
Ileum	9 (69.2%)
Cecum	1 (7.7%)
Transverse colon	1 (7.7%)
Intestinal resection	4 (30.8%)
Re-enterostomy	4 (30.8%)
Closure of enterostomy	13 (100%)[a]

Cited from "Table 4" of Ieiri S, Miyoshi K, Nagata K, Miyata J, Kohashi K, Oda Y, Taguchi T (2015) Current clinical features in diagnosis and treatment for immaturity of ganglia in Japan: analysis from 10-year nationwide survey. Pediatr Surg Int. 2015 Oct;31(10):949–54. doi: https://doi.org/10.1007/s00383-015-3774-0. Epub 2015 Aug 22

[a]Out of 13 enterostomy patients

36.2.3 Operative Findings and Surgical Procedures

Laparotomy was performed in 13 patients (86.7%). Abnormal intestinal dilatation is recognized in eight patients (61.5%), caliber change in eight patients (61.5%), and microcolon in five patients (38.5%). An enterostomy was performed in 13 patients (86.7%), an ileostomy in 9 (69.2%) patients, a jejunostomy in 2 patients (15.4%), and colostomy in 2 patients (15.4%).

The type of enterostomy is double barrel in 11 patients (84.6%), Bishop-Koop in 1 patient (7.7%), and tube enterostomy in 1 patient (7.7%). Resection of the intestine was performed in four patients (30.8%). Re-enterostomy was performed in four patients (30.8%). Closure of enterostomy was performed in 13 patients (100%, out of enterostomy patients) (Table 36.2).

36.3 Histological Examinations and Findings

AChE staining was performed in five cases (33.3%). Normal was recognized in three cases (60%) and increased AChE fibers in two cases (40%). Intraoperative rapid pathological diagnosis was performed in six patients (40%). No abnormality was recognized in two patients (33.3%). Abnormality in the intestinal ganglion cell was recognized in four patients (66.7%). HE staining was applied for all 15 patients. The

Table 36.3 Histological examinations and findings

AchE staining	5 (33.3%)
Normal	3 (60%)
Increased AchE fibers	2 (40%)
Intraoperative rapid pathological diagnosis	6 (40%)
Normal	2 (33.3%)
Abnormal	4 (66.7%)
Hematoxylin-eosin (HE) staining	15 (100%)
Immature ganglion cells	15 (100%)
Maturation of ganglion cell (specimen from closure of enterostomy)	4 (26.7%)

Cited from "Table 5" of Ieiri S, Miyoshi K, Nagata K, Miyata J, Kohashi K, Oda Y, Taguchi T (2015) Current clinical features in diagnosis and treatment for immaturity of ganglia in Japan: analysis from 10-year nationwide survey. Pediatr Surg Int. 2015 Oct;31(10):949–54. doi: https://doi.org/10.1007/s00383-015-3774-0. Epub 2015 Aug 22

sampling specimen was obtained during enterostomy, laparoscopic biopsy, and rectal full-thickness biopsy. Abnormality was recognized in 15 cases (100%), and 15 patients (100%) of which showed immature ganglion cells in HE staining. Maturation of ganglia was confirmed in four cases (26.7%) with the specimen from closure of enterostomy (Table 36.3).

36.3.1 Other Treatments

Probiotics were applied in ten patients (66.7%), Chinese herbal medicine (Daikenchu-to and Rikkunshi-to) in eight patients (53.3%), gastrointestinal prokinetic in seven patients (46.7%), and laxative in six patients (40%). Catheter-related sepsis was recognized in two patients (13.3%).

36.3.2 Prognosis and Diet

All 15 patients survived. Thirteen patients (86.7%) were treated with ordinary diet, 1 patient (6.7%) with combination of ordinary diet and elemental diet, and 1 patient (6.7%) with combination of ordinary diet and parenteral nutrition.

36.4 Summary

To identify the clinical features in diagnosis and treatment for immaturity of ganglia (IG), the data of patients with IG from the nationwide surveys in Japan were retrospectively analyzed. This survey was performed by Japanese Study Group of Allied Disorders of Hirschsprung's Disease (ADHD). In primary research, data on a total of 355 cases of ADHD were collected for 10 years (2001–2010), of which 15 patients were IG. All IG were confirmed histologically. In secondary research, detail questionnaires were sent and collected. The male-female ratio was 9:6, and the mean birth weight was 2474 g. All cases (100%) were onset in neonatal period. Primary symptoms were abdominal distention (86.7%), vomiting (53.3%), and late egestion of meconium (26.7%). An abnormal distention of intestine was recognized in 86.7% on X-ray, and microcolon was recognized in 58.3% on contrast enema. Caliber change was recognized in 58.3% on laparotomy. An enterostomy was made in 13 patients (86.7%), of which 69.2% was an ileostomy. Pathological diagnosis was performed in 100%. Enterostomy was closed in 100%.

During a 10-year period in Japan, 15 cases of IG were definitively diagnosed based on pathological findings, and almost all cases underwent surgical procedures with enterostomy. All cases had favorable prognosis. IG is an extremely rare disease. The number of incidence of IG is estimated about 1–2 patients of one million live births in Japan. But IG is an independent disease which has different clinical features in ADHD.

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Congenital Generalized Hypoganglionosis: Clinical Aspect

37

Yoshio Watanabe

37.1 Clinical Appearance

Almost all reported cases of congenital generalized hypoganglionosis (CGH) developed ileus during the neonatal period and demonstrated dilated intestinal loops in abdominal X-ray studies. The difficulty in diagnosing CGH makes it challenging to differentiate this disorder from Hirschsprung's disease (HD). CGH patients usually exhibit one or more of the following significant features: delayed passage of meconium, abdominal distension, vomiting, and displaying a transition zone on contrast enema. However, patients with HD also present with these features during the neonatal period.

In our national survey [1], 89/90 (98.9%) patients demonstrated ileus in the neonatal period, and 74/90 (82.2%) showed dilated intestinal loops by plain abdominal radiography. Radiocontrast enemas were used in 77/90 cases of the national survey, with 14 cases presenting as normal. However, nontypical findings were demonstrated; 42 patients had a microcolon, 1 had a megacolon, and 13 had caliber changes. The results of three cases were not noted, and other findings were found in six (Table 37.1).

Anorectal manometry was performed in 37/90 cases of the survey and also did not have diagnostic value, with 5 patients showing anal relaxation induced by rectal distention, while 2 had atypical relaxation, 27 exhibited no relaxation, and 3 showed unknown results (Table 37.2).

No increase of acetylcholinesterase (AChE)-positive fibers in a rectal suction biopsy appeared in most cases. Suction rectal biopsies were performed in 41/90 cases of the survey, with 32 patients showing no increased AChE activity, 6 having increased AChE activity, and 3 having no AChE activity-related data (Table 37.3).

Combined anorectal manometry and rectal suction biopsy were performed in 23/90 cases; the results of no relaxation in the manometry and no increased AChE activity in rectal suction biopsy were considered to be a high probability diagnostic method without statistical significance (Table 37.4).

Table 37.1 Findings of radiocontrast enemas in 77 cases (Duplicated findings in 2 cases)

Findings	Normal	Microcolon	Megacolon	Caliber change	Unknown	Others
No of cases	14	42	1	13	3	6

Table 37.2 Findings of anorectal manometry in 37 cases

Findings	Positive	Atypical	Negative	No data
No of cases	5	2	27	3

Table 37.3 Findings of rectal suction biopsy in 41 cases

Findings	No increase of AChE-positive fibers	Increase of AChE-positive fibers	Others
No of cases	32	6	3

Table 37.4 Combined results of anorectal manometry and rectal suction biopsy

	Positive for the manometry	Negative for the manometry
Increased AChE activity	0	4
No increased AChE activity	3	17

37.2 Initial Surgical Findings and Managements

Differential diagnosis of CGH from DH or normal intestine is difficult during initial emergency laparotomy. In the survey, the findings for 68 out of 90 CGH patients with dilated intestines and caliber changes identified during the surgery were similar to those for patients with total colonic agangli-

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onosis. A diagnosis of aganglionosis based on an intraoperative biopsy was also obtained histologically in 10/55 cases of the survey. Furthermore, there is significant difficulty in differentiating CGH from normal ganglionic intestine. Based on intraoperative histological diagnosis, 14/55 cases were classified as normal in the survey, but HCG was diagnosed following consideration of a permanent specimen.

Intestinal stomas are usually required during the initial laparotomy. In the survey, all 90 CGH cases with the exception of 1 case had stomas from the duodenum to the colon (Table 37.5). At the laparotomy, 43 cases had caliber changes at the ileum; thus, the ileum was easily selected as the initial stoma site [2]. However, there were limited improvements in bowel obstruction in patients with an ileostomy (IL). Indeed, the majority of IL cases required additional surgery to create another stoma with a shorter distance from the Treitz ligament due to persistent bowel obstruction [2]. In contrast, patients with a jejunostomy (JE) had considerable improvements in bowel obstruction, avoiding the need for both long-term fasting and further surgery during treatment of the ineffective stoma [3]. Although 6/41 IL patients were successfully treated with the initial IL only and did not require a change in stoma position, the findings of intraoperative biopsies from small limited portions of the circumference during the creation of the initial stoma in no way distinguished these cases from those that did require the creation of additional stoma [4, 5]. A JE would be recommended as the first selected position of the stoma, considering that changing treatment from IL to JE was necessary in many cases during the neonatal and infancy period [2]. Moreover, patients with stomas located less than 50 cm distal to the Treitz ligament were able to commence enteral feeding within a week following surgery [6]. Generally, patients who undergo JE, particularly upper JE, experience much more difficulty in maintaining their water balance compared to IL patients. However, output from a JE in CGH is considerably small, and patients can easily balance their intake and output due to the hypomotility of the jejunum [6].

Table 37.5 The stoma sites of all patients in the survey

	All patients (n = 90)
No stoma	1
Duodenum	2
Jejunum	40
Upper	13
Non-upper	22
No record	5
Ileum	41
Colon	5

37.3 An Important Issue During Initial Surgery

In most CGH cases, multiple biopsies of the intestinal wall were reportedly required to reach the final diagnosis, which might cause intestinal damage. Biopsy sites should be limited to a maximum of three (the middle sigmoid colon for distinguishing from HD, the distal ileum for confirmation of CGH, and the upper jejunum for both confirmation and stoma creation) to avoid damaging intestinal function. Confirmation of hypertrophic nerve strands from sigmoid colon biopsies is helpful in distinguishing CGH from HD, as the hypertrophic nerve strands, which are found in patients with HD, are absent in the sigmoid colon in CGH [7]. However, in a case of total colonic aganglionosis, it is important to note that hypertrophic nerves were reported to be prominent in the distal rectum [8]. The appendix should remain intact for future use, with an ascending enema through an appendicostomy, which is effective for the treatment of severe constipation and/or colitis due to colonic dysmotility.

37.4 Management After Creation of Stomas

The degree of whole intestinal function may be a key factor for ensuring long-term survival of CGH patients. Thus, preserving the intestine and retaining residual intestinal function to avoid future intestinal failure are essential for improved outcomes in CGH. A significant improvement in intestinal motility over time was achieved in CGH patients by intestinal manometry [9].

However, keeping gut segments distal to the JE vacant to avoid enteritis causes atrophy and gradual deterioration of the segments. Since a minimal amount of nutrients are beneficial for neonates in attempting to achieve intestinal adaptation [10], the administration of nutrients and symbiotic preparations to the distal intestine through a double-barrel JE in CGH is effective for the development of considerable function in distal intestinal segments.

Moreover, refashioning a double-barrel JE into a Bishop-Koop type JE enables the automatic administration of nutrients and symbiotic preparations to the distal intestine, regulation of intestinal flow, and prevention of an overload in the distal segment of the intestine. Treatment with GFO® and lactobacillus and refashioning to a Bishop-Koop-type JE may thus prevent future massive resection of the potentially functioning hypoganglionic distal intestine. Unnecessary removal of the malfunctioning colon is also avoidable with the habilitation procedure. The colon is important for the

absorption of minerals, especially in a case of short bowel [11]. Aerobic bacteria of the colon metabolize unabsorbed fiber to short-chain fatty acids. These fatty acids are rapidly absorbed by the colonic mucosa and used as an energy source, and this may provide additional anti-inflammatory effects [10]. In our experience, habilitation of the intestine distal to the stoma in the neonatal and early infancy period may promote both stoma closure and the weaning of patients from parenteral nutrition (PN) [6].

Further to intestinal nutrition, it is immunologically important to prevent the prolongation of fasting periods in neonates [12]. Microbial colonization of mucosal tissues during infancy plays an instrumental role in the development and education of the immune system. Recent studies have begun to define a critical period during early development in which disruption of optimal host-commensal interactions can lead to persistent and, in some cases, irreversible defects in the development and training of specific immune subsets.

37.5 Nutritional Management

A CGH patient requires PN to maintain adequate nutrition levels for growth and survival [3]. PN and its associated complications range from simple electrolyte abnormalities to life-threatening PN-associated liver disease, also known as intestinal failure-associated liver disease (IFALD). From a nutritional perspective, the ultimate goal is to provide adequate caloric intake to meet requirements and to make the successful transition from parenteral to full enteral nutrition (EN) [13]. The survey demonstrates a more efficient rate of weaning from PN to EN in both upper JE and JE patients compared with IL patients [3].

Every effort must be made to prevent catheter-related bloodstream infections in infants and children with long-term intestinal failure. Patients with dilation and dysmotility of the bowel can develop some degree of intestinal bacterial overgrowth as well as catheter sepsis [14]. Upper JE is effective in preventing intestinal stasis that can cause such overgrowth. Indeed, most deaths in the IL group occurred early in neonatal and infantile period, suggesting that these deaths were related to inadequate intestinal drainage. Thus, the release of bowel obstruction is required as soon as possible to prevent life-threatening PN-associated liver disease or sepsis caused by intestinal bacterial overgrowth. Consequently, we conclude that upper JE is the preferred treatment option in neonatal period, even in advance of a definitive diagnosis [3]. While our data analysis using the logrank test and the generalized Wilcoxon test failed to show a significant difference in the overall survival of patients, this was likely due to the insufficient number of cases (Fig. 37.1). The three JE patients who died after the 10-year (120 months) follow-up period experienced massive distal bowel resection. Fortunately, resection of distal bowel segments can be prevented by maintaining gut viability through the use of synbiotics and a Bishop-Koop type JE [6]. Avoidance of massive resection of the distal intestinal may be a key factor for ensuring long-term survival of CGH patients. Thus, retaining residual intestinal function, including immunological function, is important to avoid future intestinal failure.

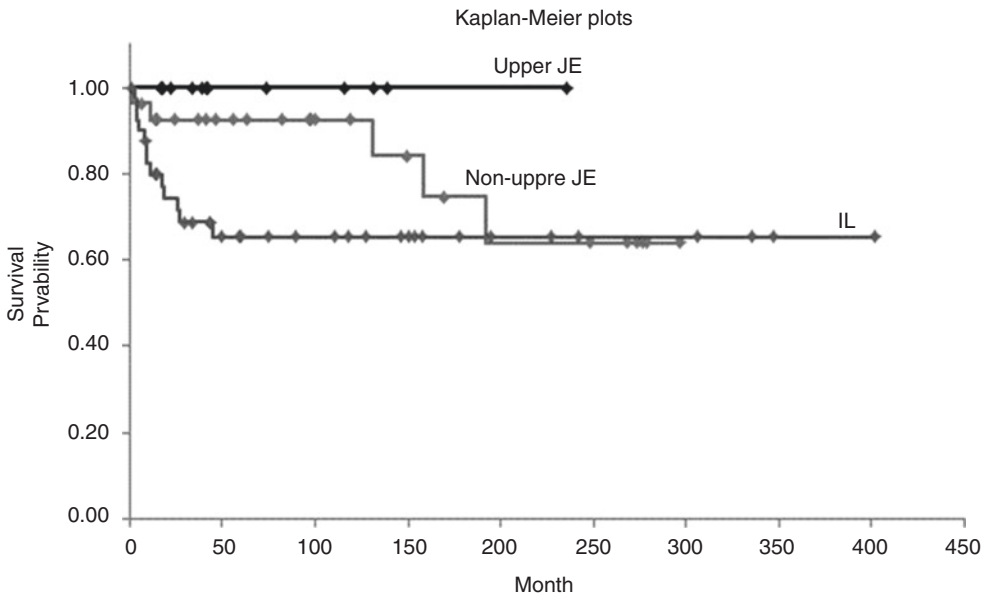

Fig. 37.1 Overall patient survival from birth to the last confirmed day of survival for upper JE, non-upper JE, and IL groups is shown in the Kaplan-Meier plots. *Upper JE* initial jejunostomy sites less than 50 cm from the Treitz ligament, *non-upper JE* initial jejunostomy sites more than 50 cm from the Treitz ligament, *IL* ileostomy

37.6 Concluding Remarks

CGH usually appeared as an emergency case with ileus in the neonatal period. Treatment is initiated by doctors in the pediatric surgical unit with limited CGH experience due to rarity of CGH. The initial surgery follows the guidelines of a HD technique. The stoma site tends to be created at the distal ileum due to the location of caliber changes in the ileum, which may not have sufficient function to release ileus. The ileus persists with prolonged intravenous treatment without EN. Enteritis due to bacterial overgrowth occurs frequently in this circumstance. A pediatric surgeon with CGH experience is then consulted after the recreation of several stomas and experience of catheter sepsis. A CGH patient misses the window of opportunity and may have remaining atrophic nonfunctioning intestine and less central venous access roots, which may cause difficulties in later treatment. The next available treatment is massive resection of the atrophic nonfunctioning intestine to control untreatable enteritis. The CGH patient will then require PN for a lifetime or intestinal transplantation. Therefore, CGH management in the neonatal and early infancy period requires special attention (Fig. 37.1).

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Isolated Hypoganglionosis, Acquired

38

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38.1 Background

Isolated hypoganglionosis (IH) is proposed to be one of the allied disorders of Hirschsprung's disease (ADHD), which is rare and resembles the symptoms of Hirschsprung's disease (HD), and associated with decreased numbers of intestinal ganglion cells [1]. Historically, the existence of this entity has been questioned [2, 3].

We previously reported that IH had two distinct entities, with different clinical characteristics and histological findings: congenital IH (C-IH) and acquired IH (A-IH) [4]. A-IH, which is characterized by its late onset, shows the particular pathological findings that are distinct from those of C-IH. And, the Japanese Study Group for Allied Disorders of Hirschsprung's Disease suggests that the following diagnostic criteria could be used to define A-IH: (1) the absence of a congenital predisposing factor; (2) the onset of symptoms after the neonatal period; (3) the degeneration of ganglion cells, decrease in ganglion cell numbers, and gliosis in Auerbach's plexus with the preservation of the size of the plexus; and (4) a satisfactory outcome after the resection of the involved intestine.

38.2 Nationwide Survey of Allied Disorders of Hirschsprung's Disease in Japan

In the present nationwide retrospective cohort study, which was supported by the Ministry of Health, Labour and Welfare, Japan, preliminary questionnaires were sent to the 161 major institutes of pediatric surgery or gastroenterology (representing the core members of the Japanese Society of Pediatric Surgeons, the Japanese Society of Pediatric Nutrition, Gastroenterology, and Hepatology, and the Japanese Study Group of Pediatric Constipation). The questionnaires asked about the number of ADHD cases that were treated from January 2000 to December 2009. Replies were obtained from 157 out of the 161 institutes (98%). A total of 355 ADHD cases were collected [5]. We found five cases of A-IH regarding the criteria described above. Then, we sent secondary questionnaires that asked about the background characteristics, the clinical and pathological findings, and the treatments and outcomes of each case of A-IH. Based on the results of the secondary questionnaire, we collected the clinical and pathological information of five cases of A-IH and investigated the details.

38.3 Epidemiology and Diagnostic Tools of A-IH

Of five cases with A-IH, the male to female ratio was 3:2.

With the exception of two cases (case 2: necrotic enterocolitis in neonate, case 3: influenza encephalitis in early childhood and mental retardation), none of the patients had a specific past medical history before the onset of symptoms. The onset of symptoms occurred in infancy (n = 1, case 2), early childhood (n = 1, case 3), and childhood (in school-age children; n = 3, cases 1, 4, and 5). The initial clinical symptoms were chronic constipation (n = 2, cases 1 and 4), abdominal distension (n = 1, case 2), and abdominal distension and vomiting (n = 1, case 5); one case showed intestinal perforation and vomiting (case 3) (Table 38.1).

The onset of the symptoms of A-IH patients in the present study occurred at various ages in childhood after the neonatal period (from infants to school children); the main symptom was constipation, which was prolonged and gradually progressive. In contrast, the onset of symptoms in patients with C-IH is in the early neonatal period, and the symptoms of C-IH include severe abdominal distension and intestinal

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Table 38.1 The characteristics and examination results of each case of acquired isolated hypoganglionosis

Case no.	1	2	3	4	5
Sex	Female	Male	Male	Male	Female
Past medical history	None	Necrotic enterocolitis in neonate	Influenza encephalitis Mental retardation	None	None
Onset of symptoms	School-age	Infant	Early childhood	School-age	School-age
Primary symptoms	Chronic constipation	Abdominal distension	Vomiting Intestinal perforation	Chronic constipation	Abdominal distension Vomiting
Associated malformations	None	None	None	None	None
Chromosomal abnormalities	None	None	None	Not examined	Not examined
Family history	Prader-Willi syndrome	None	None	None	None
Abdominal X-ray image	Abnormal intestinal dilatation	Abnormal intestinal dilatation/air-fluid level	Free air	Abnormal intestinal dilatation	Air-fluid level
Contrast enema	Megacolon	Normal	Not examined	Megacolon	Megacolon
Rectosphincteric reflex	Negative	Not examined	Positive	Positive	Unknown
Rectal mucosal biopsy	Normal	Not examined	Not examined	Normal	Unknown

obstruction after ileostomy in the neonatal period [5, 6]. Thus, the onset and symptoms of A-IH seem different from those of A-IH.

The abdominal X-ray images showed abnormal intestinal dilatation (n = 3, cases 1, 2, and 4), air-fluid level (n = 2, cases 2 and 5), and free air (n = 1, case 3). Contrast enema showed megacolon (n = 3, cases 1, 4, and 5) and normal results (n = 1, case 2); contrast enema was not conducted in case 2 because of the bad condition. Three cases underwent anorectal manometry, which indicated rectosphincteric reflex positivity (n = 2, cases 2 and 3) and negativity (n = 1, case 1). Two patients underwent rectal mucosal biopsy; the findings were normal in both cases (Table 38.1).

38.4 The Extent of Involved Segments of A-IH

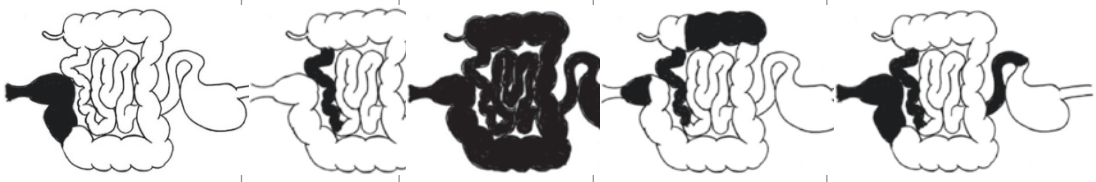
The intestinal segments that were involved in the cases with A-IH in the present study were wide-ranging (Table 38.2). In line with the observations of a previous report [4], the lesions seemed like "skip segments," spreading from the stomach to rectum. A previous systematic review showed that the involved intestinal segments of C-IH were localized, from total intestinal to rectosigmoidal (especially colonic) [6]. In contrast, Watanabe et al. reported the operative findings of 90 cases of C-IH and noted the presence of dilated intestine with caliber changes starting at the small intestine in 63 cases [6], indicating that the involved location spreads subtotally from the small intestine to the rectum in patients with C-IH.

38.5 Managements and Outcomes of A-IH

Initially, except for case 3 with immediate surgical intervention due to intestinal perforation, all four cases were managed with conservative medical treatment; however, their conditions did not improve. Finally, all five patients underwent multiple operations (average: 4.6 operations per case) because multiple intestinal segments were affected. The procedures included creation of enterostomy, resection of the involved segments of the dilated intestine, and/or pull-through because the involved segments spread from the stomach to the rectum (partially or totally) in each case (Table 38.2). Currently, all five cases are alive, and two enteric fistulas remain. All but one of the patients are capable of ingesting a general diet without the need for parenteral feeding (Table 38.2).

Although the A-IH patients required multiple operations which were similar to those required by C-IH patients, their postoperative outcomes were far better. In C-IH, dysmotility does not improve over time, re-enterostomy was required in most cases, and the combination of continuous parenteral nutrition and partial enteral nutrition was necessary for the patients to survive [4]. On the other hand, while the A-IH cases in the present study required multiple operations, satisfactory outcomes were eventually obtained, with the oral

Table 38.2 The surgical treatments and outcomes of each case

Case no.	1	2	3	4	5
Involved segment	**Sigmoid colon-rectum**	**Ileum**	**Stomach-anus**	**Ileum, ascending colon, rectum**	**Duodenum, ileum, sigmoid colon-rectum**
					
Total number of operation	**7**	**3**	**5**	**3**	**6**
Pull-through	2	0	0	1	2
Resection of dilated intestine	0	0	0	0	1
Creation of enterostomy	3	2	1	0	0
Resection of dilated intestine and enterostomy	0	0	1	0	0
Others	2	1	3	2	3
Histological findings from the resected intestine	**Hypoganglionosis/ sigmoid colon and rectum**	**1st: Normal/ ileum 3rd: Decrease of ganglion cells/ileum**	**1st: Normal/ ileum 3rd: Decrease of ganglion cells and gliosis/ileum**	**Decrease of ganglion cells, immaturity/ sigmoid colon and rectum**	**Chronic inflammation with decrease of ganglion cells, degeneration of ganglion cells/ileum**
Outcome	**Survived**	**Survived**	**Survived**	**Survived**	**Survived**
Current nutrition	Ingestion of general diet	Ingestion of general diet	Ingestion of defined formula diet with parenteral nutrition	Ingestion of general diet	Ingestion of general diet
Remaining enteric fistula	Yes	No	Yes	No	No

Histological findings and outcome are important issues and are represented in bold

intake of a general diet without the need for parenteral nutrition in all but one of the patients.

38.6 Histopathological Findings of A-IH

On the resected specimens, hematoxylin and eosin (H&E) staining revealed that all five cases had ganglion cell degeneration and decreased ganglion cell numbers with a normal size Auerbach's plexus in the resected intestine (Fig. 38.1); however, it should be noted that in two of the five cases, the numbers and sizes of ganglion cells were normal at the first resection. Immunohistochemical staining, which was performed using HuC/D, S-100, and SOX10 antibodies, was effective in identifying the remaining ganglion cells, the preservation of the size of Auerbach's plexus, and the increased glial cell numbers in the plexus (Fig. 38.2).

In the description regarding hypogenetic-type C-IH reviewed by Friedmacher et al. [7], the number of ganglion cells decreases, and the size of plexus is also small. In the present study, all of the patients with A-IH showed ganglion cell degeneration and decreased ganglion cell numbers, while the size of Auerbach's plexus was preserved. These findings are similar to the previous report in which the size of Auerbach's plexus was normal, whereas ganglion cell degeneration, decreased ganglion cell numbers, and the proliferation of glial cells were prominent [4]. The report also noted that these findings were evidence that ganglion cells were initially present and that they gradually disappeared. In the present study, in two out of the five cases, the size and the number of ganglion cells were normal at the first resection, and then the ganglion cell numbers decreased. Therefore, it is possible that some factors may affect the ganglion cells [4].

Chagas disease, an infection caused by the protozoan parasite *Trypanosoma cruzi*, is known to cause the degeneration and decrease of ganglion cells. Previous reports on colonic involvement in Chagas disease patients have described particular pathological features such as the degeneration of the intrinsic myenteric neurons and a decrease in

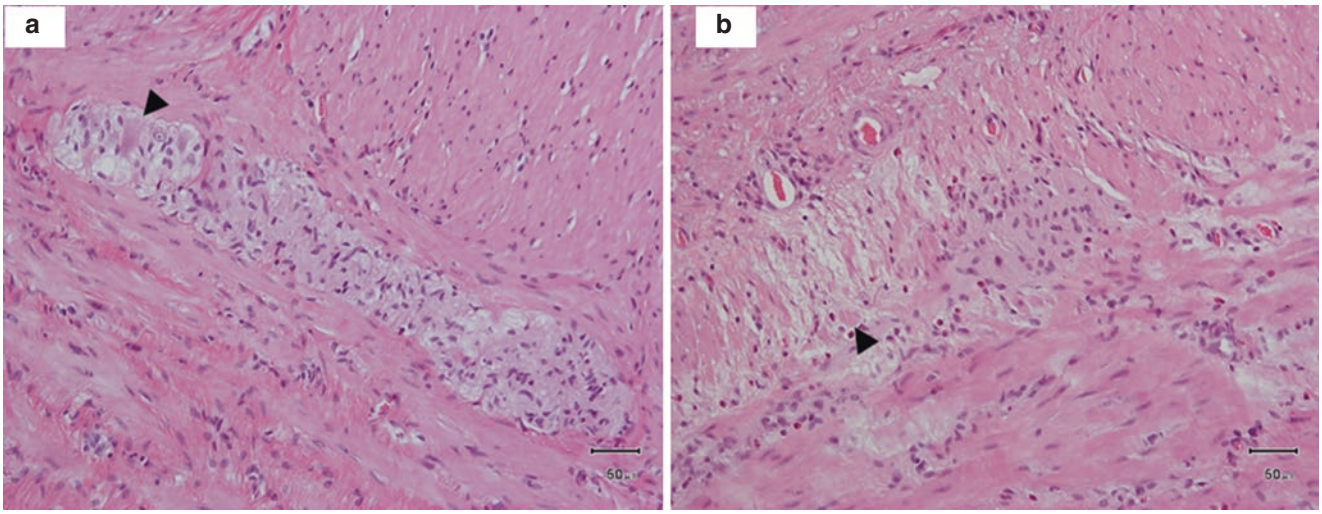


Fig. 38.1 The typical pathology of acquired isolated hypoganglionosis (case 5). (**a**) The colon. The plexus shows a mixture of almost normal ganglion cells and gliosis. (**b**) The ileum. The ganglion cells have disappeared, and glial cells increased. Arrowheads indicate degenerated ganglion cells; hematoxylin and eosin staining

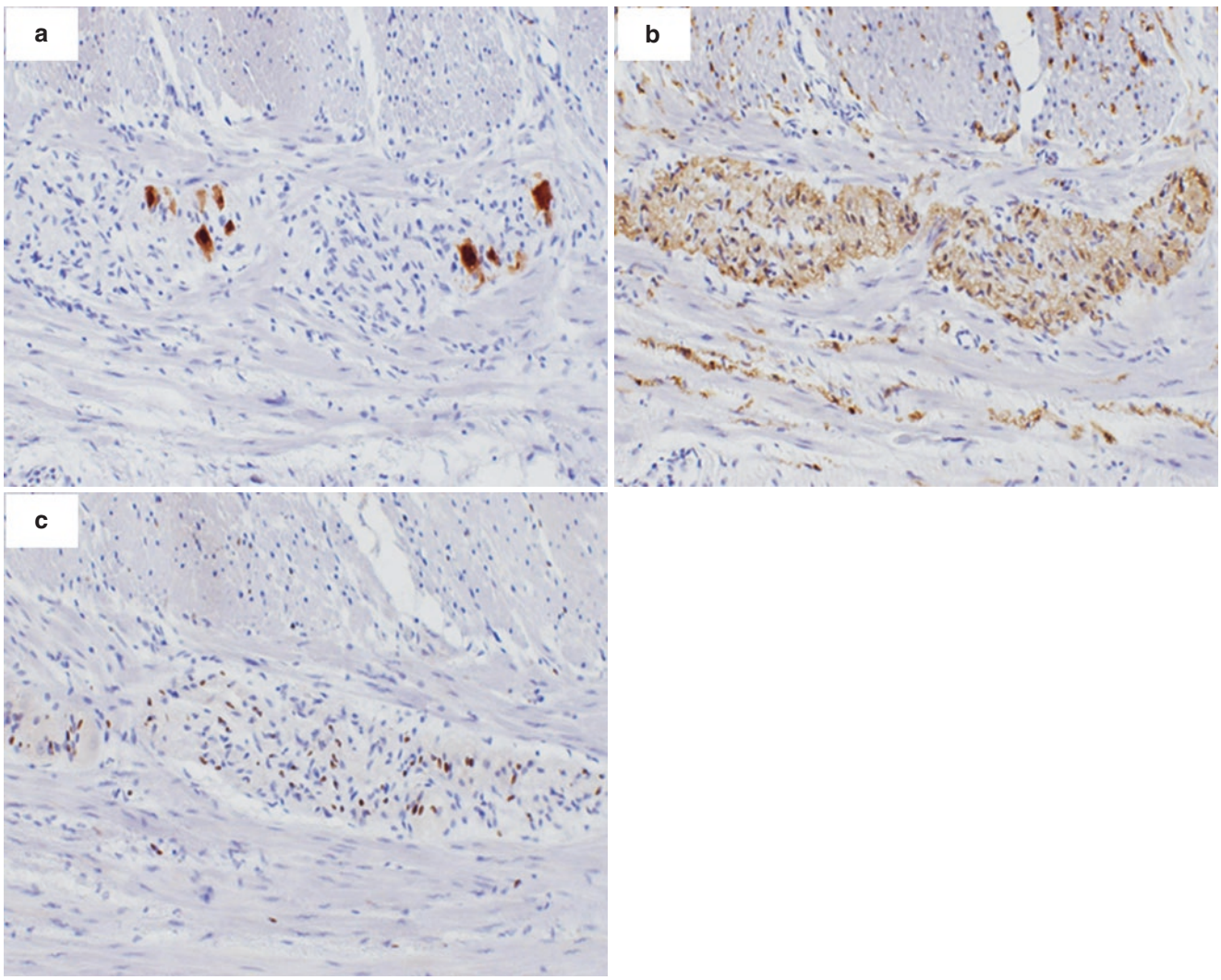


Fig. 38.2 The immunohistochemical findings in a patient with acquired isolated hypoganglionosis (case 5). (**a**) HuC/D immunostaining. (**b**) S-100 protein immunostaining. (**c**) SOX10 immunostaining. HuC/D immunostaining highlights the indistinguishable ganglion cells in the increased glial cell numbers in the plexus. S-100 protein is panneuronal marker and shows the size of enteric plexus. Glial cells were positively stained by SOX10

their numbers, as well as reduced numbers of nitric oxide-containing myenteric neurons, deficiency of the interstitial cells of Cajal, T lymphocyte-induced ganglion cell damage, increased fibrosis, and increased numbers of mast cells [8]. The results of the previous reports [4] and the present study suggest that factors which are causative of A-IH, such as severe chronic constipation, chronic enterocolitis due to chronic constipation, peritonitis due to intestinal perforation, or infection, might exist, in other words, the degeneration of ganglion cells and decrease in their number might occur secondary to prolonged constipation, systemic shock, or intestinal ischemia on the involved intestines.

38.7 Conclusion

The findings of the present study prove that A-IH is a rare but distinct entity. The pathological characteristics include a decrease in ganglion cell numbers and gliosis and the preservation of the size of Auerbach's plexus. The onset of symptoms occurs in patients of various ages. The clinical outcome after the resection of the involved intestine, which usually shows dilatation, is considered to be favorable. Patients with A-IH may require multiple operations due to the varying extent of the associated lesions.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. And, for this type of study, formal consent was not required. This retrospective study was also approved by the ethics committee for clinical research of Kyushu University Hospital (No. 28-155).

Conflict of interest: None.

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Intestinal Neuronal Dysplasia (IND)

39

Fumi Alicia Ishida and Hiroyuki Kobayashi

39.1 Introduction

Intestinal neuronal dysplasia (IND) is a pathological condition in which hyperplasia of the submucosal and myenteric plexuses occurs, causing clinical symptoms resembling that of Hirschsprung's disease despite distinct histological differences. Reports of IND occurring independently, or isolated IND, vary between 0.3% and 62% of all suction rectal biopsies worldwide [1]. In addition, IND can occur in conjunction with other gastrointestinal neuropathies. This condition in which IND coexists with another gastrointestinal disorder is referred to as associated IND. IND is typically associated with Hirschsprung's disease (HD), and the reported incidence varies from 20% to 66% [2]. Moreover, Fadda et al. further separated IND into two distinct subtypes based on both clinical and histological conditions. These subtypes are referred to as IND Type A and IND Type B [3].

Although there have been numerous papers categorizing various cases of IND, in particular IND Type B, lack of clarity in diagnostic criteria and methodology among pediatric surgeons and researchers has caused IND to remain a controversial topic with regard to its existence as a distinct histopathological entity since IND was first proposed in 1971 [4]. Some pediatric surgeons in Europe and Asia claim that there is sufficient evidence to support the existence of IND, while some pediatric surgeons in the United States in particular remain unconvinced. Despite a myriad of publications on IND, the etiology and mechanisms of IND still remain unclear. In addition, due to lack of specific diagnostic criteria, pediatric surgeons and researchers are continuously striving to develop and improve diagnostic criteria based on current scientific data in order to reach a consensus on IND. Further research is still needed to better understand the mechanisms underpinning IND in order to develop better diagnostic procedures, prevention measures, and treatment methods and improve the quality of life of patients with IND.

39.2 History

In 1958, Ravitch coined the term "Pseudo-HD" in order to describe conditions which appear clinically identical to HD but, in fact, have discrete pathological entities [5]. Currently, allied disorders of Hirschsprung's disease (ADHD) or, according to Ravitch, "Pseudo-HD" is used to describe a group of clinical conditions that mimic Hirschsprung's disease (HD) but have ganglion cells in the terminal rectum as opposed to being aganglionic [6]. In other words, despite having clinical symptoms that are difficult to distinguish from HD, ADHD encompasses distinct pathological characteristics, leading researchers and pediatric surgeons to treat disorders under ADHD as a separate entity from HD [7].

In 1958, Ravitch elaborated on the term ADHD by suggesting disorders grouped within ADHD be referred to as "Pseudo-HD." Ravitch chose this term "Pseudo-HD" in order to illustrate the fact that "Pseudo-HD" appears clinically identical to HD but, in fact, has discrete pathological entities.

In 1971, Meier-Ruge was the first to formally describe one of the diseases from the ADHD or according to Ravitch, Pseudo-HD class of diseases. This disease became formally known as IND. Meier-Ruge defines IND as a disease that clinically resembles HD, but with distinct histological features, including hyperplasia of the submucosal and myenteric plexuses and increased acetylcholinesterase (AChE) activity in the lamina propria [1]. Subsequently, Puri refined the term ADHD by categorizing IND, among other neurogastrointestinal disorders, under a division known as "variants of Hirschsprung's disease" in 1997 [8]. Variants of Hirschsprung's disease (VHD) is comprised of eight different

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neurogastrointestinal diseases and grouped into two different categories: disorders associated with abnormal ganglia and disorders with normal ganglia. According to the criteria suggested by Puri et al., IND falls under the category of disorders with abnormal ganglia. Furthermore, Friedmacher et al. also reported a case of associated IND, in which IND was found in conjunction with HD [9].

In Japan, Okamoto and Toyosaka tweaked Ravitch's term "Pseudo-HD" by developing their own criteria for disorders to fall under this categorization. According to the authors, "Pseudo-HD" disorders display congenital, nonmechanical obstructions of the intestine and also entail the presence of intramural ganglion cells in the terminal rectum [10]. Similar to Puri et al., Okamoto and Toyosaka further divided these disorders into two groups based on histological findings of abnormal or normal ganglia and placed IND in the abnormal ganglia division [7].

39.3 Etiology

Although the mechanisms that underlie IND are still not fully understood, some etiological evidence has been found in support of the existence of IND Type B by some pediatric surgeons and researchers. For instance, there have been numerous familial reports of IND, implying that there may be a genetic aspect of IND Type B [9]. One study looked at the effects of IND Type B on monozygotic twins, whereas another study found several family members with multiple generations of histopathological evidence of IND Type B. Furthermore, IND Type B has been identified in some families with other associated congenital gastrointestinal tract abnormalities. All of these studies suggest that there may be a genetic component to IND [11].

Furthermore, a few studies have identified possible genes involved in the development of IND. For instance, Yamataka et al. conducted an experiment using animal models, which allowed them to pinpoint the Ncx/Hox11L1 gene as a potential important player in the development of IND. In this study, the Ncx/Hox11L1 gene, which is typically expressed in a subset of the neural crest of embryones between 9.5 and 13.5 days, was knocked out to create homozygous mutant Ncx/Hox11L.1 (Ncx−/−) deficient mice. Electrical stimulation-induced contractile response of the intestine in the knockout mice showed relaxation-dominant patterns that appear to be due to the presence of nonadrenergic, noncholinergic nerves. This data suggests that mice with the knockout Ncx/Hox11L.1 gene may have a form of varied gastrointestinal nerve supply. Moreover, this study found that mice with this mutation developed a myriad of pathologies that affected bowel motility. The mega-ileo-ceco-colon, or mega-ICC, along with changes in the proximal colon was especially seen in these mice. The results of this study suggest that the Ncx/Hox11L1 could be an important gene that may cause or contribute to the development of IND [12].

Although numerous animal studies have come closer to pinpointing the genetic workings that influence the development of IND, mutations in specific genes, such as RET, glial cell line-derived neurotrophic factor (GDNF), and other selected genes that have been associated with HD have not yet been found in patients with IND. Moreover, researchers still have not determined whether the changes seen in IND are a variant of normal bowel development or a secondary acquired phenomenon caused by inflammation [9].

A study conducted by Kobayashi et al. investigated this controversial topic of IND. The purpose of this experiment was to determine if IND is a primary disorder of the parasympathetic innervation or ganglion cell migration or if it can develop as a secondary hyperplastic phenomenon caused by obstruction or inflammation. Put more simply, Kobayashi et al. strived to discover whether or not IND is a primary or secondary condition or possibly both. This study was the first to report histopathological changes resembling IND in response to persistent enterocolitis brought about by postoperative complications of surgical treatment for HD. In this study, researchers looked at the surgical specimens of a total of 36 patients who underwent complete resection of the aganglionic portion of the bowel. Although associated IND was not detected on initial examination, 2 out of 36 patients displayed histological findings similar to IND postoperatively. These patients displayed hyperganglionosis with giant ganglia as well as increased AChE activity in the mucosal layers. The results from this study suggest that IND can develop in previously normal bowel as a reaction to inflammation associated with chronic enterocolitis. The data also suggests that IND appears to have a spectrum of histopathological changes that depend on the severity and duration of enterocolitis. In addition, Kobayashi et al. found that after enterocolitis heals, histological changes also occur in which giant ganglia disappear completely. The underlying mechanism of this change is still not fully understood. Although additional research is still required to further investigate the correlation between inflammation caused by enterocolitis and the degree of histological changes that occur in response to inflammation, this study provides strong evidence that IND may develop as a secondary phenomenon to inflammation [13].

In another study conducted by Sacher et al., the debate on whether IND should be considered a primary or secondary disorder was further examined. The observation that human neonates with intestinal obstructive lesions tend to display histology similar to IND led Sacher et al. to hypothesize that IND is a pathology secondary to intestinal obstructive lesions. Sacher et al. conducted an experiment to test this hypothesis and determine if a rat model subjected to intestinal obstruction will develop histology similar to IND. This

experiment showed that although IND histology was found in human neonates with intestinal obstructive lesions, similar prolonged intestinal obstruction in rats did not cause the same development of IND histology. Because these rats did not develop histology similar to IND, the authors concluded that IND may not be a secondary disorder to intestinal obstructive lesions. Further support that IND may not be a secondary disorder to intestinal obstructive lesions is that many patients who are treated for chronic constipation, and therefore experience intestinal obstructive lesions, do not display pathological features of IND after conducting rectal suction biopsies. The contrasting data of the human neonates who developed IND after experiencing intestinal obstructive lesions and the rat neonates who did not develop IND makes the distinction of IND as a primary or secondary disorder still unclear [14]. The hypothesis that histological attributes of IND may develop as a secondary reaction to processes such as intestinal obstructive lesions and inflammation have become a popular topic among researchers in order to further delve into the mechanisms that are responsible for the occurrence of IND.

Further research is still essential in order to discover additional mutations that may cause IND and, therefore, form a better understanding of the genetic etiology of IND. The etiology of IND still remains unclear because the underlying mechanisms appear to be diverse, including developmental disturbances, reactive changes, or inflammatory diseases. Malformations that lead to the development of IND most likely have combined malformations, which make deciphering the exact mechanisms of IND even more difficult to determine.

39.4 Clinical Condition

The majority of IND patients have accompanying symptoms of chronic constipation with or without abdominal distention [9]. Fadda et al. divided IND into two separate subtypes: IND Type A and IND Type B, with IND Type B being the more common of the two and accounting for about 95% of patients with IND [7]. IND Type A cases are quite rare, occurring in less than 5% of patients with IND. These patients typically exhibit symptoms of abnormal distension, bowel obstruction, and episodes of diarrhea in addition to hemorrhagic stools. In regard to histology, patients with IND Type A typically display congenital aplasia or hypoplasia of the sympathetic innervation of the myenteric plexus [2, 7]. IND Type A is also typically found during the neonatal period. Symptoms of chronic constipation, such as delays in the meconium passage, abdominal distension, vomiting, and failure to thrive, may begin in the first few years of life [15]. By contrast, the more common IND Type B is defined as a disorder with hyperplasia of the parasympathetic plexus of the myenteric and submucosal plexuses. Giant ganglia are another common feature of IND Type B [2, 7]. Additional histological features of IND Type B include ectopic ganglion cells and increased AChE activity in the lamina propria and around submucosal blood vessels as well [1]. Patients with IND Type B display symptoms similar to those of HD. Associated IND is also always considered to be IND Type B [1].

Recently there has been an increase in the number of adult IND Type B cases as well. Some adult patients with IND Type B exhibit symptoms of severe chronic constipation from a young age. By contrast, some of these adult patients develop symptoms in adulthood. In addition to symptoms of chronic constipation and abdominal distension, some patients develop rare yet severe conditions such as enterocolitis, bowel obstruction, volvulus, and intussusceptions [15].

Because the clinical presentations of IND Type B can potentially be misdiagnosed as other neurointestinal disorders such as HD, histological examination of rectal biopsies is essential for accurate diagnosis.

39.5 Diagnosis

One of the main reasons for the controversy surrounding IND is the lack of consistent diagnostic criteria among pediatric surgeons and researchers. Different diagnostic criteria among pediatric surgeons have caused highly contrasting incidences of IND across various centers around the world. In order to address this issue, the diagnostic methods and criteria for IND have been continuously improved upon since the first description of IND in 1971 by Meier-Ruge. These developments are made with the aim to create a more consistent and reliable diagnostic criteria to enable researchers and pediatric surgeons around the world to make a more accurate diagnosis and universal definition of IND.

Initially, abdominal X-rays can be used to look for evidence of a distended bowel, and abdominal computed tomography scans can be used to detect signs of mechanical obstruction. However, X-rays and abdominal computed tomography are not sufficient to form an accurate diagnosis of IND, due to the fact that HD and ADHD also display similar signs of mechanical obstruction. In order to avoid misdiagnosis, further examination is required in the form of rectal biopsies. There are two forms of rectal biopsies: full-thickness biopsy and suction rectal biopsy. Each biopsy may provide variable histological information, which could potentially lead to differing diagnosis and thus necessitate pediatric surgeons to choose a common procedure. Typically a suction biopsy technique is used as a primary form of diagnosis because it is a simple procedure and does not have many biopsy-related high risk factors such as bleeding and

bowel perforation. Full-thickness biopsies are conducted if the results of the suction biopsy show abnormal findings. Full-thickness biopsies allow for the analysis of deeper and wider tissues but impose higher risks of bleeding, scarring, and bowel perforation.

Biopsy specimens may be frozen and further analyzed through the use of staining protocols such as H&E staining and acetylcholinesterase (AChE) staining.

Currently, the main diagnostic criteria for IND Type B are hyperplasia of the submucosal plexus along with the presence of giant ganglia, hyperganglionosis, and increased acetylcholinesterase activity around submucosal vessels [15]. Meier-Ruge expanded on this algorithm by stating that IND Type B can only be diagnosed if more than 20% of all ganglia in the submucosa contain nine or more ganglion cells. Furthermore, because ganglia size and AChE activity in the lamina propria mucosa are age dependent, it would not be appropriate to diagnose a child younger than 1 year old with IND because infants under 1 year old may contain immature giant ganglia, increasing the possibility for misdiagnosis. This has led to the second criterion that patients must be older than 1 year old in order to be eligible for diagnosis of IND [7].

In 1998, Lumb and Moore conducted an experiment to determine whether giant ganglia are in fact an appropriate diagnostic criterion for IND. The results from this study suggest that giant ganglia may not be an appropriate criterion for the diagnosis of IND because the authors discovered giant ganglia in segments of the large intestine that had been resected from patients who had colorectal carcinoma. Lumb and Moore believe that this data proposes that because giant ganglia can be found in conditions other than IND, it is not an appropriate determining criterion for the diagnosis of IND [16].

Since this study, differing evidence by other researchers has proven to be in favor of utilizing giant ganglia as an important diagnostic factor for IND. In 2014, Taguchi et al. carried out a 10-year retrospective cohort study in which a nationwide survey was conducted to determine the number of actual cases of IND Type B in Japan according to the newest diagnostic algorithm proposed by Meier-Ruge. After reviewing a total of 355 surveys of patients diagnosed with ADHD nationwide, Taguchi et al. discovered that four patients met the current criteria for IND Type B, suggesting that IND Type B is a distinct entity that should be considered separately from other neurogastrointestinal disorders. Taguchi et al. also determined that giant ganglia (Fig. 39.1) are essential for the diagnosis of IND. This is due to the fact that although a majority of patients displayed histochemical evidence of increased AChE fibers and ectopic ganglia, all patients showed giant ganglia in the submucosa [7].

Swaminathan et al. built upon the findings of this Japanese survey in their own study, which utilized a different form of study methodology and what they believe to be a more appropriate sample pool. This study focused on the criterion of giant ganglia as the determining factor and analyzed the histochemical data of full-circumference paraffin sections from proximal margins of pull-through resection specimens. These samples were obtained from patients with HD and compared to autopsy controls with no history of intestinal dysmotility. Each paraffin section was immunostained for the neuron-specific Hu antigen and counterstained with hematoxylin. The nucleated ganglion cells in each submucosal ganglion were counted sequentially. Each observer was able to count the amount of ganglion cells by utilizing a microscope and shifting the field of view over the full-circumference of the tissue section. This procedure allows each observer to calculate the total number of submucosal ganglia, number of ganglion cells in each ganglia, and relative distribution of smaller and larger ganglia around the circumference. Researchers found that ganglion cells can be easily identified and quantified with good reducibility by each observer [17]. One disadvantage found is that submucosal ganglion cell counts from the same sections differ significantly between each observer, meaning that interobserver variability may be an issue with potential observer bias. Although interobservability appears to be an issue, the results of this study suggest that with specific techniques, giant ganglia can easily be quantifiable [17].

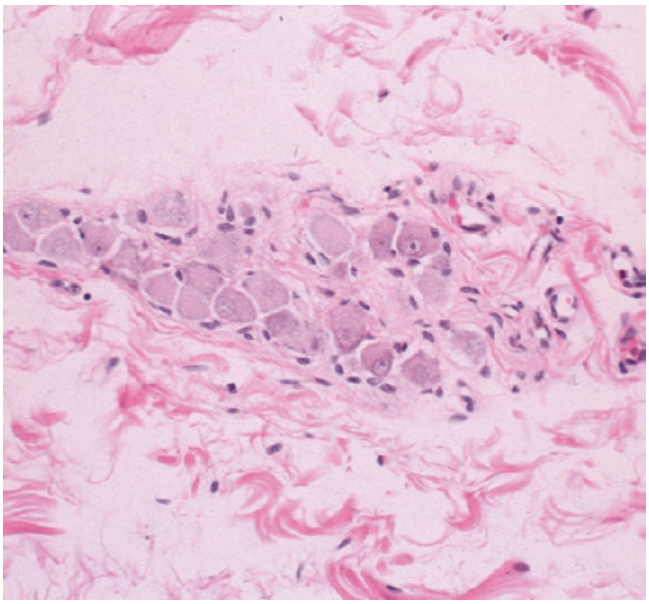

Fig. 39.1 Giant ganglia (containing nine or more ganglion cells) in submucosa (H&E staining ×200)

Further research is still required to determine uniform and specific laboratory conduct across researchers around the world, such as staining methods, section thickness, and counting procedures, in order to develop a proper diagnostic algorithm for IND.

39.6 Treatment

Understandably, treatment for IND also remains uncertain due to the lack of clarity about the pathogenesis and diagnosis of IND. Patients with IND typically undergo a myriad of different treatment procedures that vary from conservative management to surgical procedures depending on the severity of the case [11].

Most patients begin on a conservative treatment course, which focuses on alleviating the symptoms of chronic constipation. Some of these treatments may include dietary changes, laxatives, and enemas [11]. In 2004, Schimpl et al. reported satisfactory outcomes in a follow-up period of 7.2 years in 80% of 105 patients diagnosed with IND who were treated with dietary changes, cisapride, laxatives, and enemas [11]. Another report states that conservative treatment of IND has been effective in 33–64% of patients with IND [15].

Ideally, patients can be successfully treated with conservative techniques. But in some cases, conservative procedures may not be enough to alleviate symptoms. If necessary, surgical treatment is also an option if conservative methods do not appear to be effective after 6 months. Unfortunately, a unified concept for the surgical treatment of HD has been developed, but IND, at this current time, does not have one. Because of this, surgeons perform a variety of surgical treatments. Some of these procedures include transabdominal procedure, temporary loop colostomy, or, in severe cases, a subtotal colectomy and ileorectal anastomosis may be performed [15]. A myectomy of the internal anal sphincter has also been performed with satisfactory results [9]. Other clinicians recommend a resection of the impacted bowel segment and pull-through procedures.

39.7 Discussion

Although there is a long history of reports of IND, researchers and pediatric surgeons have yet to form a consensus on the diagnostic criteria and laboratory methods needed in order to efficiently and accurately diagnose IND. Current data suggests that the main determining factor for the diagnosis of IND may lie in the finding of submucosa giant ganglia, which is currently defined as a ganglion containing nine or more nerve cell bodies in a single tissue section, according to Meier-Ruge's newest diagnostic algorithm update [17]. Further research is needed to develop a uniform and accurate description of IND. In order to reach this ultimate goal, it is vital to discover if IND is a primary or a secondary disorder, or possibly both, determine an appropriate sample pool, and come to a consensus about the main determining factors of IND. It is necessary for current data and methodologies to be shared accurately and specifically among research centers around the world. In addition, improved laboratory methods and specific technical formalities, such as staining and counting procedures, must be determined to formulate a specific and solid definition of IND. It is important that pediatric surgeons have access to reliable information to not only accurately diagnose but successfully treat patients with IND and ultimately improve overall quality of life.

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Megacystis Microcolon Intestinal Hypoperistalsis Syndrome: MMIHS

40

Hideki Soh

40.1 Introduction

Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is a rare congenital functional intestinal obstruction. This syndrome is characterized by abdominal distension, a largely dilated nonobstructive bladder, microcolon, and severe functional intestinal obstruction without structural atresia or stenosis in the neonatal period [1, 2].

In 1976, Berdon et al. firstly reported five newborn patients that presented with small intestinal nonorganic obstruction, microcolon, and megacystis [1]. All of the patients represented severe defective intestinal peristalsis, and parenteral nutrition (PN) was required for their entire lives (1 day to 34 months old). In three of the patients, an autopsy revealed normal ganglion cells throughout the entire bowel. The authors documented that the hypoperistalsis was largely refractory to pharmacologic treatment, and the etiology was unknown. Since then, cases of MMIHS have been reported sporadically [3–8].

Currently, there is no specific treatment for this condition [3–5]. In MMIHS patients, the gastrointestinal hypoperistalsis prevents oral feeding and the toleration of enteral nutrition. Most of the patients have to be maintained by PN, which often leads to life-threatening complications. The etiology of this syndrome remains unclear. And effective treatment is not established, and the prognosis is still poor.

40.2 Pathogenesis

MMIHS is classified as a disease without abnormality in the ganglion cell histologically in allied disorders of Hirschsprung's disease, like the chronic intestinal pseudo-obstruction (CIPO). It is characterized by normal ganglion cells found in intramural plexus of the gastrointestinal tract [9]. Subsequently, numerous case reports have been published, and various hypotheses have been proposed to describe the pathogenesis of MMIHS: genetic, neurogenic, myogenic, and hormonal origin [9–11]. However, the etiology of this condition remains unclear.

Rudolph et al. reported the gamut of chronic intestinal pseudo-obstruction in children, in which MMIHS was categorized into visceral myopathy [9]. Some investigators attempted to classify MMIHS as neurogenic or myogenic [10–12]. The majority of reports regarding MMIHS has not shown the specific histologic findings in the muscle layers of the bowel and bladder wall [4].

Piotrowska et al. reported absence of intestinal cell of Cajal (ICCs) in the bowel and urinary bladder of patients with MMIHS [13]. ICCs are pacemaker cells that assist active propagation of electrical events and neurotransmission, and their absence may result in hypoperistalsis and voiding dysfunction in MMIHS.

Other investigators have reported absence or marked reduction in α-smooth muscle actin and other contractile and cytoskeletal proteins in the smooth muscle layer of MMIHS bowel. Contractile and cytoskeletal proteins are important structural and functional of SMCs and play a vital role in the interaction of the filaments in smooth muscle contraction [11, 13].

Puri et al. showed vacuolar degenerative changes in the smooth muscle cells (SMCs) with abundant connective tissue between muscle cells in the bowel and bladder of patients with MMIHS and suggested that a degenerative disease of smooth muscle cells could be the cause of this syndrome [14].

Other some works suggested that the absence of functional subunit containing neuronal nicotinic acetylcholine receptor (ηAChR) may provide a possible explanation for the underlying pathogenesis of MMIHS [15–17].

Recently, ACTG2-related disorders are reported as a subset of visceral myopathy with variable involvement of the bladder and intestine. Fifty-three families with ACTG2 mutation have been reported, and many of them were

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described afflicted with megacystis and recurrent intestinal obstructions [18]. It is expected to apply noninvasive gene analysis to clinical practice for diagnosis of MMIHS and CIPO in neonates, children, and adults [19].

40.3 Etiology

According to the systematic review by Gosemann et al., although the incidence frequency is not known in detail, it is extremely rare, 227 cases in 35 years from 1976 to 2011 [5]. In a national survey conducted in Japan by Taguchi et al., only 19 cases were enrolled in the decade from 2001 to 2010 in Japan. It is one of the rare refractory diseases [20].

In the published data so far, several authors agree that there is a female predominance for MMIHS. In the first report by Berdon et al., all five cases were girls [1], and Puri et al. reported that the ratio of male to female was 1:2.41. It is common in girls even in Japan.

Nineteen sets of siblings affected with MMIHS were reported. Eighteen families had two affected siblings and one had three. Four sets of affected siblings occurred to consanguineous parents [2, 21–23].

40.4 Symptoms

The clinical symptoms of MMIHS are characterized by abdominal distention, delayed passage of meconium, bile-stained vomiting, and abdominal distention similar to other neonatal intestinal obstructive disease.

Functional intestinal obstruction due to peristalsis disorders of the gastrointestinal tract. And hypoperistaltic lesions are observed diffusely in a wide range from the jejunum and the ileum to the rectum in most cases.

Since the state of intestinal peristaltic dysfunction persists chronically, the symptoms of bowel obstruction are prolonged, and in some cases concomitant enteritis occurs. The intestines are diffusely dilated and sometimes causing strangulation. Therefore, it is difficult to establish oral feeding or enteral nutrition, and most cases require parenteral nutrition for a long period. In most cases, symptoms are progressive, and the prognosis is poor.

Other, neurogenic bladder and hydronephrosis have been reported as a failure of the urinary system caused by the huge bladder.

Gosemann et al. reported 61 cases of 182 had bilious vomiting, and failure to pass meconium was clearly reported in only 23 cases in review [5]. The majority of patients were not able to void spontaneously. And it is needed to relieve the microcolon and the distended nonobstructed urinary bladder by contrast examination or ultrasound examination in MMIHS patients. In this disease, the presence of neonatal intestinal obstruction symptoms and microcolon and megacystis is directly linked to the diagnosis. So it is necessary that all these symptoms are complete in MMIHS patients.

Chronic intestinal hypoperistalsis will be sustained for long time; intestinal obstruction symptom is prolonged in many patients. Enteritis repeats and becomes more severe in some case. The intestines are often dilated chronically, so in few cases the dilated bowel twists and strangles. In most cases establishing oral feeding and enteral nutrition is difficult, and total parenteral nutrition is required for long term [20]. And many patients receive an enterostomy for decompressing the bowel. These symptoms are progressive in many cases.

40.5 Diagnosis

MMIHS is diagnosed by the intestinal obstruction symptoms due to hypoperistalsis and the presence of microcolon and giant bladder in the neonatal period. Several diseases that present similar symptoms in neonatal periods are known as differential diagnosis, for example, ileal atresia, total colon aganglionosis, and isolated hypoganglionosis. Histopathological examinations of the full-thickness intestinal specimens are mandatory for the definitive diagnosis of MMIHS. The conventional histological examination, such as H&E staining, exhibits no abnormalities in the ganglion plexus of the affected intestine and failed to show the meaningful pathologic findings.

Some previous reports have described fetal ultrasound findings associated with MMIHS. Puri et al. reviewed 54 cases of ultrasound findings associated with MMIHS reported in the literature [5]. The most frequent finding was enlarged bladder (88%), with hydronephrosis seen in 31 patients (57%). Normal amniotic fluid volume was revealed in 32 cases (59%), increased volume in 18 (33%), and decreased volume in four (7%). In 3 of 51 cases (5%), abdominal distention caused by dilated stomach was detected. Three cases of oligohydramnios during the second and early third trimesters were reported, probably related to the functional bladder obstruction. In one case, oligohydramnios changed into polyhydramnios at the end of the third trimester.

40.6 Radiological Findings

Usually radiological evaluation is necessary and useful for diagnosis of MMIHS. Plain abdominal films show dilated fixed small intestine loops and niveau, similar to other intestinal obstruction diseases. And gasless image is often observed in the pelvic cavity (Fig. 40.1). However, it is difficult to diagnose MMIHS only with abdominal X-rays. In

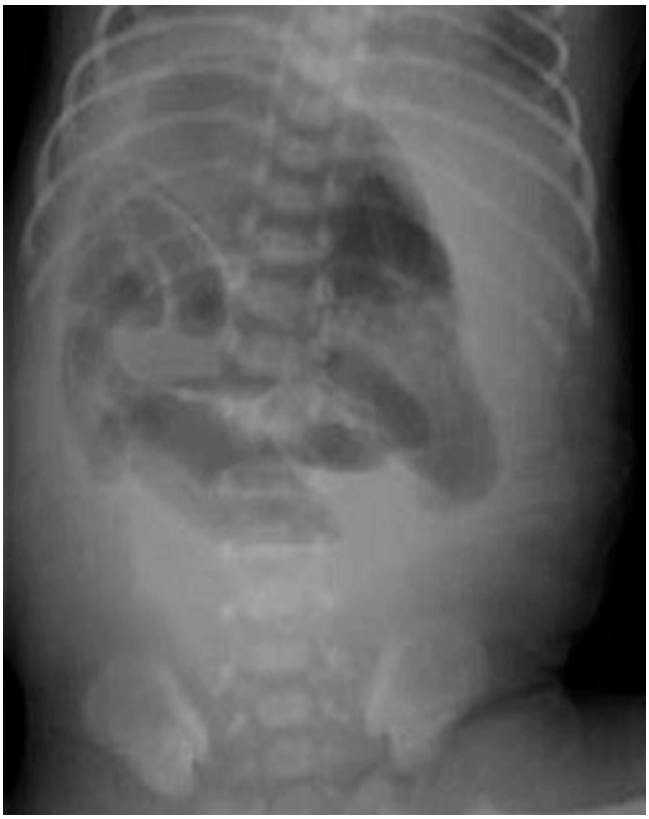

Fig. 40.1 Abdominal X-ray of newborn girl with MMIHS showing gas of the dilated intestine and niveau

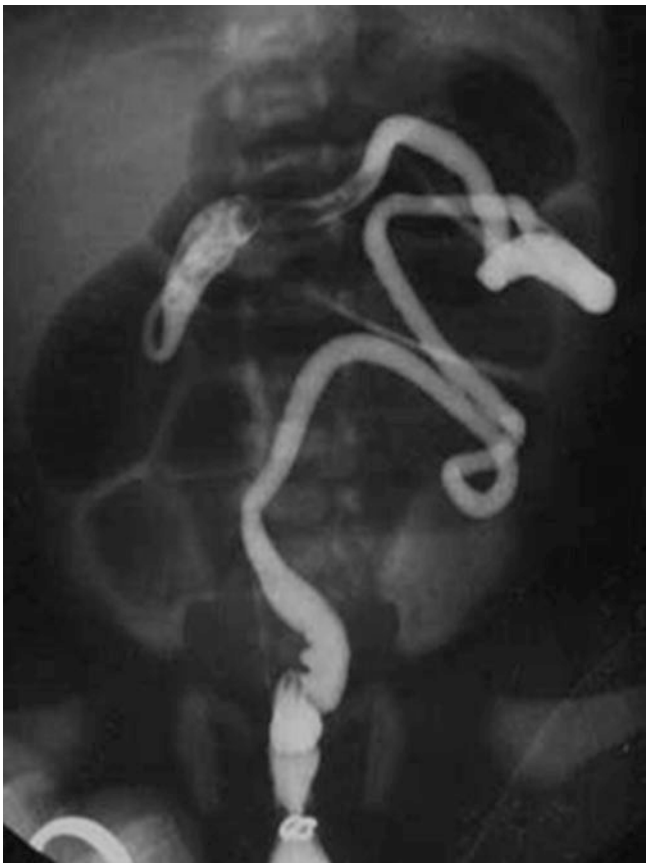

Fig. 40.2 Contrast enema of four-day-old girl with MMIHS showing microcolon

addition to it, it is necessary to visualize a microcolon by enema examination (Fig. 40.2).

These two tests alone may be difficult to differentiate from other diseases such as total colon aganglionosis and ileal atresia. Cystography or ultrasound sonography showed an enlarged bladder. Vesicoureteral reflux and hydronephrosis are pointed out in cystography in some cases.

Nonetheless, it is often difficult to prove that there is no organic obstruction by only radiological examinations, and in the final diagnosis, it requires examination by laparotomy as described below.

In many cases, ileal atresia can be distinguished from MMIHS by symptoms and radiological findings. Also long segment aganglionosis is diagnosed by absence of ganglion with H&E histological examination via laparotomy. However, it is sometimes difficult to differentiate from other allied disorders of Hirschsprung's disease. Clinically, the presence of microcolon and giant bladder is the decisive factor in diagnosis. Differentiation from isolated hypoganglionosis is performed by histological diagnosis. It may be difficult to differentiate from severe CIPO. In the case of abdominal distension and biliary vomiting in neonatal period, it is recommended strongly that enema radiography and bladder contrast or ultrasonography should be performed.

40.7 Histopathological Finding

In most cases of MMIHS, abdominal distension is so severe. Laparotomy is performed often in neonatal period. Exploratory laparotomy was necessary to decompress the severely dilated intestine and to rule out congenital anomalies, such as intestinal atresia and long segment aganglionosis. Exploratory laparoscopy could therefore be chosen in patients, who do not need emergent intestinal drainage, in order to reduce the morbidity and complications associated with laparotomy in newborns. Furthermore, histopathological examinations of the full-thickness intestinal specimens are mandatory for the definitive diagnosis of MMIHS and the initial management in newborns who have intestinal obstruction and microcolon.

In most reported cases of MMIHS, the ganglion cells were normal in terms of the appearance and number [20]. Accordingly, full-thickness pathological examinations should be performed for all of the patients. As mentioned above, most of MMIHS patients showed no abnormalities in the ganglion plexus of the affected intestine using H&E staining histological examination.

40.8 Treatment

The management of patients with MMIHS is frustrating. In the majority of reports, surgical interventions of the gastrointestinal tract have generally been unsuccessful and did not improve intestinal pseudo-obstruction or bladder function. Mainly to decompress the intestinal system, gastrostomy, jejunostomy, ileostomy, and cecostomy are chosen. In Japanese study, 16 of the 19 patients (84%) required intestinal decompression with permanent enterostomies [20]. However no therapeutic interventions, including either medication or surgery, improved the outcomes [3–5]. Several authors now agree that the decision for surgical interventions should be made carefully, individualized, and in most cases restricted to supportive interventions. There are some reports that medication, such as a prokinetic drugs, and synbiotics had been useful in the alleviation of the symptoms. However they were not definitive ones, and parenteral nutrition is required in most cases.

Currently, symptomatic and palliative treatments may play a key role in MMIHS therapy, including intestinal decompression and nutritional support, although long-term PN sometimes leads to life-threatening complications.

These findings confirm that pediatric MMIHS is a serious and intractable disorder and is likely to significantly minimize a patients' quality of life. Further studies on the management of MMIHS are required to establish reliable medical and surgical therapies, including small bowel transplantation. Gosemann et al. reported that 12 of 227 patients with a diagnosis of MMIHS received multivisceral transplantations [5]. The indications of small bowel or multivisceral transplantation need to be discussed based on the systematic analyses of many cases of this condition [13, 14, 18].

40.9 Outcome

In 2011, Gosemann and Puri reported a systematic review of outcomes of MMIHS [5]. In this systematic review, 80% of children with MMIHS died. Only 23 of the 182 reported patients were alive, the oldest being 18 years old. Twenty-one of the 23 patients were being maintained by total or partial parenteral nutrition. The need for surgical intervention should be made carefully and individualized, in that most explorations have not been helpful and probably are not necessary. They mentioned that advances in the management of intestinal failure, including optimal nutritional support and improvements in sepsis control, could prolong the survival of the patients.

In Japanese national survey [20], 42% (9/19) of children diagnosed as MMIHS died of enteritis or sepsis. Liver dysfunction was noted in 16 patients (84%) and was considered to be related to the complex pathogenesis of PN, enteritis, and sepsis in 14, 6, and 7 patients, respectively. The cause of death was liver failure in six patients, sepsis in one patient, and the causes of death were not clarified in the remaining two patients. Nine patients (42%) between the ages of 6 months and 14 years old (median 2.3 years) died, and ten were alive at the time of the survey and were between the ages of 2.1 and 24.1 years old (median 8.8). Eight of the ten survivors (80%) depended predominantly on PN, and the remaining two patients were maintained with enteral feeding. Of the ten survivors, four (40%) had liver dysfunction, another developed more than ten catheter-related blood stream infections, and eight had a drainage stoma.

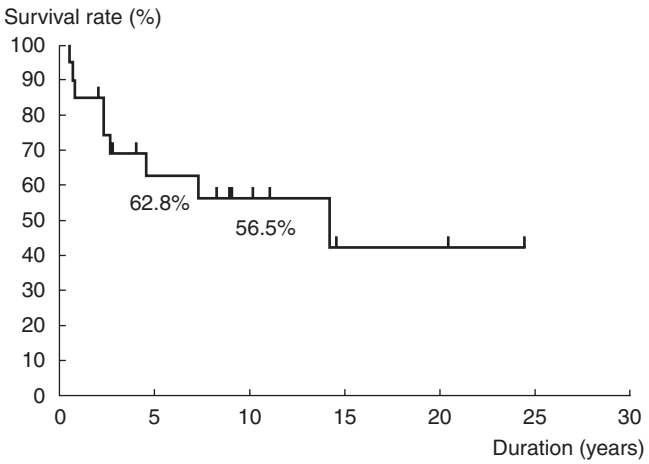

Fig. 40.3 The survival rates of MMIHS in Japan obtained from 19 patients using the Kaplan-Meier Method. The 5- and 10-year survival rates were 63% and 58%, respectively

In this report, the survival rates of the 19 patients with MMIHS were analyzed using the Kaplan-Meier method (Fig. 40.3). The 5- and 10-year survival rates were 63% and 57%, respectively. One-third of the MMIHS patients died within the infantile or toddler period. The prognosis of MMIHS was severely poor. In comparison with the reports of isolated hypoganglionosis and CIPO based on the same nationwide survey in Japan [13, 14], the prognosis of MMIHS was much poorer than that of these two conditions.

40.10 Summary

MMIHS patients develop severe functional intestinal obstruction in the neonatal period, and, currently, there is no specific therapeutic intervention, including medication and surgery. The majority of MMIHS patients require long-term PN and drainage stomas. Small bowel or multivisceral transplantation may be necessary to improve the outcomes of MMIHS.

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Internal Anal Sphincter Achalasia (IASA)

41

Shigeru Ueno

41.1 Historical Aspect

41.1.1 Concept of Internal Anal Sphincter Achalasia (IASA)

As early as 1900, spasm of the internal sphincter was thought to be responsible for idiopathic megarectum associated with severe and prolonged constipation. It was Hurst in 1934 who thought that the pathogenesis might involve failure of the internal sphincter to relax rather than anal spasm and suggested the term anal achalasia [1]. On the other hand, after establishment of entity of Hirschsprung's disease in 1948 by Swenson and his colleagues as a surgically correctable one in patients with severe constipation, the narrow segment of the intestine is the cause of the disease, and its resection can be the definitive treatment [2]. Diagnosis of the disease had been based on the histological confirmation of the aganglionosis after surgical rectal biopsy [3] before manometry was introduced as a nonsurgical test for the diagnosis [4]. In normal subjects, transient distention of the rectum with a balloon produced reflex relaxation of the internal sphincter. In patients with Hirschsprung's disease, there is no reflex of the internal sphincter or may have contraction instead, while in patients with idiopathic megacolon, internal sphincter responses were normal (Fig. 41.1a, b). Thus, the abnormal response or failure of relaxation found in Hirschsprung's disease is characteristic and not of megacolon in general [5–8].

Concept of internal anal sphincter achalasia (IASA) was first described by Davidson and Bauer in 1958 [9]. They said at the introduction of the paper: "In the classifications of the causes of constipation, at one extreme is the surgically amenable congenital aganglionic megacolon, Hirschsprung's disease, and at the opposite pole are the children with severe emotional disturbances. Although variations in the extent of involved colon in Hirschsprung's disease were pointed out, biopsy of the terminal achalasic aganglionic segment should reveal absence of ganglia of the myenteric plexuses. Similarly, the clinical picture of the psychogenic constipation is fairly clear-cut and quite different from that of Hirschsprung's disease. Symptoms usually do not begin at birth and the colon is filled with stool down to the internal anal sphincter and biopsy should reveal ganglia in all areas."

In their reported three cases, however, there was difficulty in distinguishing psychogenic constipation from aganglionosis. They had had constipation since birth and presented with fecal impaction and soiling. No definite "collapsed" or narrow segment of the distal colon was demonstrated on barium enema. They used acetylbetamethylcholine (Mecholyl®), a potent parasympathetic drug, to induce colonic movement and recorded the intraluminal pressure in lower portion of the rectum. With each injection the colon displayed the proximal relaxation but no relaxation distally. Their motility data indicated that they would have aganglionosis, while barium enemas revealed moderately dilated rectum without any zone of narrowing, which was interpreted as not giving any evidence of Hirschsprung's disease, except one of them had a rectal "shelf." All three patients underwent pull-through surgery after resection of a length of bowel extending from the sigmoid to the rectum and appeared cured. Histological study of the specimen revealed the presence of ganglia in all areas. They summarized that a short area of achalasia proximal to the anus was demonstrable by motility studies and that surgical resection of the achalasic segment resulted in improvement. They described the condition as "achalasia of the distal rectal segment."

In the 1970s, there are several papers from Germany about chronic constipations in children. Holschneider and others emphasized the presence of anal sphincter achalasia, which was demonstrable by manometric study as Fig. 41.1c. In their papers chronic constipation in children was considered due to a functional asynchronism of the internal and external anal sphincter relaxation reflexes, and the term "neurovegetative or myogenic achalasia of the anal sphincter"

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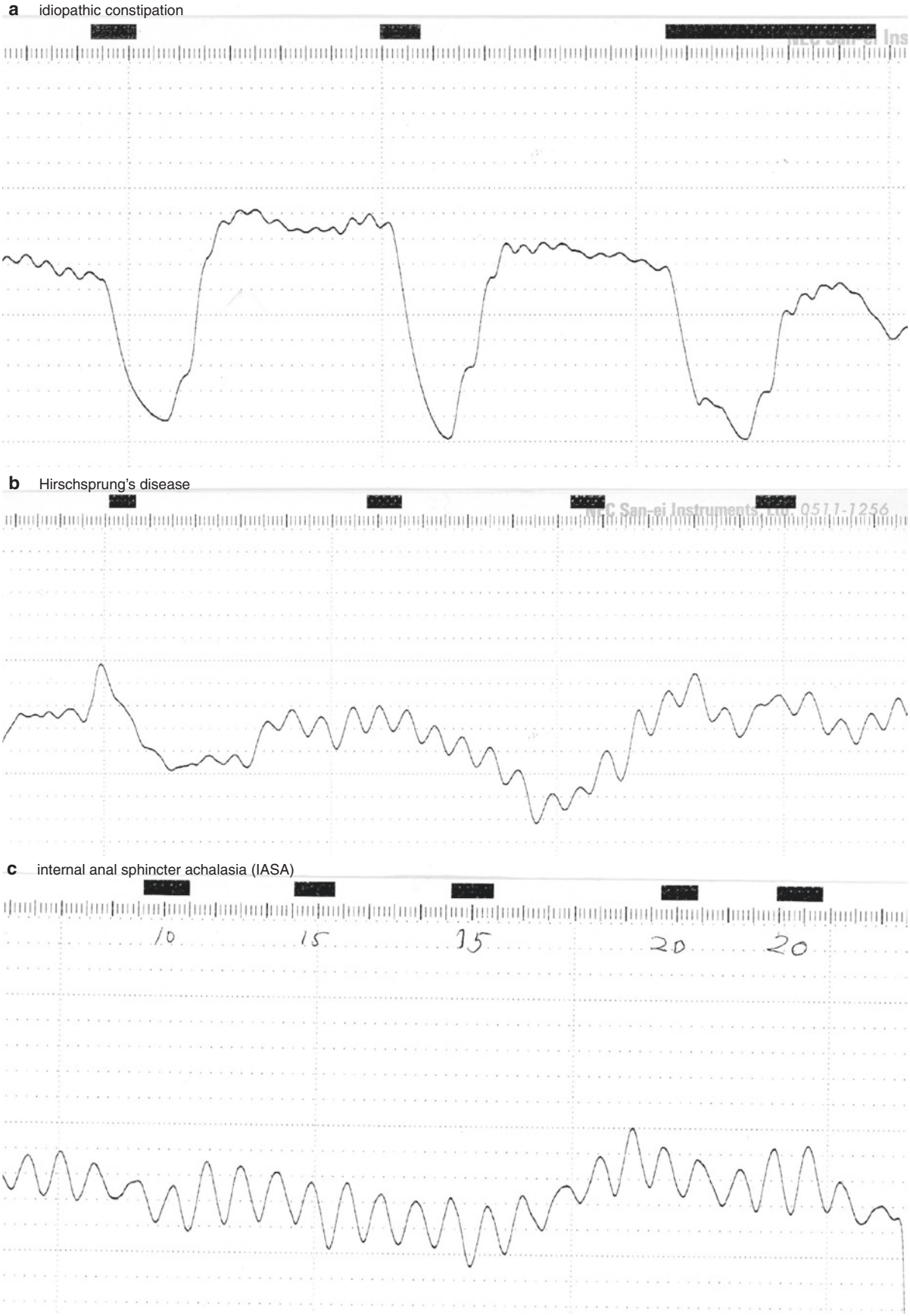

Fig. 41.1 Pressure profiles of the internal sphincter of a patient with idiopathic constipation (**a**), one with Hirschsprung's disease (**b**), and one with IASA (**c**). Solid bar indicates dilatation of the rectum by a balloon

to describe their pathogenesis was used [10, 11]. Meister reported that 104 out of 148 constipated children had achalasia of the anal sphincter and the achalasia was functional in 62 cases and organic in 42 cases. He suggested three causes of organic achalasia: myogenic, neurogenic, and neurovegetative. In patients with myogenic achalasia, he found inflammation with fibrosis, fibrosis only, and muscular hyperplasia. Patients with neurogenic achalasia all had colonic aganglionosis (Hirschsprung's disease). In those with neurovegetative achalasia, slight inflammation, fibrosis, or essentially no pathologic findings were observed [12].

41.1.2 Ultrashort Segment Hirschsprung's Disease

Although Davidson and Bauer did not mention the term "ultrashort Hirschsprung's disease (aganglionosis)" in their paper [9], a short area of achalasia proximal to the anus demonstrable by motility studies was considered as a very short segment of aganglionosis, which should be attributed to the failure of relaxation in those patients. Since then, the diagnostic label of ultrashort Hirschsprung's disease has prevailed in the literature to define a spectrum of conditions with clinical presentation like Hirschsprung's disease but with presence of ganglion cells on rectal biopsy [1].

In 1966 Bentley reported his experience on the treatment of children with megarectum who have failed to respond to prolonged medical management of chronic constipation and of infants with recurrent impaction without anal stenosis by anorectal excisional myectomy. He examined histologically 22 myectomized specimens and categorized them into three groups: seven with normal histology, ten with Hirschsprung's disease, and five with abnormalities in the myenteric plexus without complete aganglionosis. He mentioned that there are difficulties in differentiating idiopathic or psychogenic accumulation of feces from atypical ultrashort segment Hirschsprung's disease, which is defined as aganglionosis of the distal third of the rectum or less [13].

On the other hand, Aldridge and Campbell reported that there is "hypoganglionic" zone in the terminal rectum based on an autopsy study of 22 normal infants [14]. The presence of ganglion cells in the rectum biopsied was explained as representing biopsy sites proximal beyond that area. This was especially thought to be likely in small infants where the rectum is proportionately shorter [15].

After the pathogenesis of megarectum in chronically constipated patients that could be attributed to this entity, several papers reporting significant numbers of patients with ultrashort Hirschsprung's disease were published where the authors arbitrarily included patients into this category and presented the disease as "ultrashort" segment aganglionosis of the terminal rectum [16, 17]. In 1990, Neilson and Yasbek reported five cases with this category and proposed criteria for the diagnosis of ultrashort Hirschsprung's disease [1]. There criteria include (1) chronic constipation from birth or early childhood, (2) abdominal distension or fecal soiling and the presence of stool in rectal ampulla, (3) presence of ganglion cells on suction rectal biopsy at 3 and 5 cm from anal verge, (4) barium enema without transition zone typical of Hirschsprung's disease, (5) manometry showing failure of anorectal reflex with prolonged internal sphincter contraction after transient rectal distention, and (6) clinical improvement after anal myomectomy with the presence of ganglion cells on myomectomy specimen.

Meier-Ruge and Scharli, who suggested performing biopsies at the pectinate line and then proximally at 1, 2, and 4 cm, made a clear distinction between an ultrashort segment of 1–3 cm and segments over 4 cm, with the latter cases representing classical Hirschsprung's disease. They also reported distinctive histochemical characteristics between them. In ultrashort Hirschsprung's disease cases, massively increased acetylcholinesterase (AChE) activity was confined to the fibers of the muscularis mucosae while in classical Hirschsprung's disease, nerve fiber networks even more conspicuous in the lamina propria mucosae [18, 19].

41.1.3 Histochemistry and Neuronal Intestinal Dysplasia (NID) and Others

After understandings of the gastrointestinal motility and molecular mechanisms made progress and histopathological methods have developed, pathological findings upon myectomized internal sphincter muscles from patients with chronic constipation have been reported. Fadda et al. surveyed the internal sphincter specimens obtained from patients with achalasia undergoing sphincter myectomy by enzyme histochemically and found three different features. When the internal sphincters were obtained from Hirschsprung's disease patients, they were aganglionic, and increased acetylcholinesterase (AChE) activity was found. In cases diagnosed to have neuronal dysplasia, the specimen contained increased numbers of ganglionic neurons and increased activity of AChE. In their study, they called it normal internal sphincter when isolated ganglion cells are sometimes present but often missing in sections containing little smooth muscle, while few AChE-positive nerve fibers are present [20].

41.2 Entity of IASA

41.2.1 Diagnostic Criteria of IASA

Neilson and Yasbek concluded that ultrashort Hirschsprung's disease is a reality but it is only one cause of anal achalasia and proposed that until the pathogenesis of this condition is

elucidated, the term ultrashort Hirschsprung's disease should be replaced by anorectal achalasia [1]. In the consensus workshop entitled "Criteria for Classification and Diagnosis of Dysganglionoses" held in 2004 by most recognized experts in this field, participants agreed on the issue of Internal Anal Sphincter Neurogenic Achalasia that the diagnosis of the entity is the result of clinical, manometric, and histochemical studies. Moreover, none excluded manometry as enzymatic histochemistry, and histology alone cannot provide the diagnosis [21].

In 2009, Doodnath and Puri published a review about IASA where definite diagnosis of IASA is based on (1) anorectal manometry that shows the absence of rectosphincteric reflex on rectal balloon inflation and the presence of marked rhythmic activity of the IAS and (2) the presence of ganglion cells and normal AChE activity in the rectal suction biopsy [22].

41.2.2 Pathophysiology of IASA

Many authors investigated about pathophysiology of internal sphincter obtained from patients diagnosed to have internal anal sphincter achalasia. As early as in 1973, Baumgarten reported decreased purinergic inhibitory neurons in the specimen [23]. Meier-Ruge and others reported distinctive features of type B neuronal intestinal dysplasia in the internal sphincter muscle presenting achalasia [17, 18]. Ariel et al. reported a case with hypoganglionosis of the myenteric plexus with normal Meissner's plexus and intranuclear inclusion bodies in Schwann cells [24]. Ueno et al. reported a case with clinical features of IASA associated with granular-cell tumorlike Schwann cell degeneration in the myectomized anal sphincter [25]. Puri and his colleagues vigorously investigated the myectomized IASA specimens and observed abnormal peptidergic innervation [26], depletion of NADPH-diaphorase activity [27, 28], reduced neural cell adhesion molecules, decreased neuromuscular junction proteins (PGP 9.5, synapsin I) [29], and altered distribution of interstitial cells of Cajal [30]. However, they mentioned in their review that the exact pathogenesis and pathophysiology of IASA is not fully understood [22].

41.2.3 Incidence of IASA or Ultrashort Segment Hirschprung's Disease

If internal anal sphincter achalasia can be referred to ultrashort segment Hirschsprung's disease, the incidence of this entity has been reported in many literatures as the incidence of ultrashort in a series of patients with Hirschsprung's disease, although this form of Hirschsprung's disease had received too little attention up until the 1970s [10]. In 1971, Nissan and Bar-Maor were only able to find 38 patients in the literature who had a histologically confirmed ultrashort segment, although this disorder had been described as early as 1934 by Hurst [31]. After recognizing this entity, children with long-standing chronic constipation without internal sphincter relaxation on manometry with the presence of ganglion cells have been categorized into "ultrashort" segment aganglionosis.

In a review of 501 cases of Hirschsprung's disease by Swenson et al., an incidence of 7.5% of cases could be described as ultrashort segment [16]. The high incidence of ultrashort segment can be attributed to an increased awareness of the condition and referral for investigation of patients who had been attending hospital for many years with constipation. Clayden and Lawson reported that among 106 who had failed to respond to a trial of medical treatment for constipation, 10 (9%) were considered to have ultrashort segment Hirschsprung's disease, which was confirmed on histology [32]. Some claimed the ultrashort as distal third of the rectum or less [12], and Orr and Scobie reported patients with ultrashort Hirschsprung's disease as much as 15% of all Hirschsprung's disease patients [17]. Meier-Ruge and Schärli reported that ultrashort segment Hirschsprung's disease accounted for about 10% of all the cases of aganglionosis of the rectum and rectosigmoid encountered using enzyme histochemical analysis [18, 19].

When chronic constipation was used as the basic disease, De Caluwe et al. reported that the incidence of internal anal sphincter achalasia is 4.5% among 332 children who were investigated for chronic constipation [33]. Bagdzevičius et al. reported 2 out of 44 children with megarectum were diagnosed with ultrashort-segment Hirschsprung's disease by acetylcholinesterase histochemistry [34].

However, in Japan, the entity of ultrashort Hirschsprung's disease or internal anal sphincter achalasia has not been recognized despite manometric study has been widely used to evaluate children with chronic constipation. Iwai et al. reported that the anorectal reflex was absent in all nine of the patients with Hirschsprung's disease while in all of ten patients with idiopathic megacolon rectal distension produced a relaxation in the anal canal like that of the normal subjects [6]. Ohashi et al. recognized the chronically constipated patients with simple megarectum but found that most of them had significantly high anal canal pressure and "incomplete" anal relaxation after rectal stimulation on manometry. They only called these findings as hypertonic and achalasic sphincter and proposed "high anal pressure syndrome" for such patients [35].

Recently, a nationwide retrospective cohort study of the allied disorders of Hirschsprung's disease including questionnaires to 161 major institutions and Japanese literature

search about IASA were carried out. Obata et al. reported only five patients with definitive IASA were found by this vigorous survey [36].

41.3 Is IASA a Reality or Not?

41.3.1 Diagnostic Methods for Chronically Constipated Patients

In Japanese nationwide survey for Hirschsprung's disease, which accumulated 1087 patients, a contrast enema was used for the diagnosis of Hirschsprung's disease in almost all the patients (99.2%), but manometry was performed less frequently in 45.8% of them, while a rectal mucosal biopsy with acetylcholinesterase (AChE) staining was used for 81.8% of patients [37]. In Europe, in the workup of patients with suspected Hirschsprung's disease, all respondents (100%) perform rectal biopsies, 96% request a contrast enema, and 31% do anorectal manometry. Rectal biopsies are obtained using the suction technique by 61% respondents and via open full-thickness by the other 39% respondents; the number of specimens that are routinely taken is three by 55% [38].

In this current situation, when a patient with long-standing constipation is suspected to have Hirschsprung's disease, rectal suction biopsies would be performed after contrast enema. If ganglion cells are present with normal AChE activity in the biopsied specimen, should we go on to investigate the patient by manometry to see if he/she has IASA? Or should the patient be diagnosed to be idiopathic and treatment for chronic functional constipation be continued?

To answer this question, we need to consider how to recognize this entity after reviewing the significance of rectal manometry and normal anatomy of the terminal rectum.

41.3.2 What We Need to Know: Anorectal Manometry (ARM) and Anatomy of the Terminal Rectum

The term achalasia merely denotes a functional disturbance involving muscle spasm and says nothing about morphology. Internal anal sphincter achalasia (IASA) can be defined as a clinical condition presented like Hirschsprung's disease with the presence of ganglion cells in the intramural plexus of the terminal rectum and without relaxation of the anorectum or internal anal sphincter in response to dilatation of the rectum (absence of the rectosphincteric reflex). When there is a segment of the rectum without any ganglion cell, it can be called Hirschsprung's disease or congenital intestinal aganglionosis. As some authors like Meier-Ruge and Schärli or Ikawa et al. emphasized, staining for acetylcholinesterase (AChE) of rectal biopsy material is the most reliable way of diagnosing Hirschsprung's disease however short it is [18, 19, 39].

Diagnosis of IASA is the result of a clinical, manometric, and histochemical studies, and it should not exclude manometry as enzymatic histochemistry, and histology alone cannot provide the diagnosis, as agreed in the consensus workshop in 2004 [21]. If the criteria for IASA proposed by Doodnath and Puri can be agreed [22], it should be diagnosed based on (1) anorectal manometry that shows the absence of rectosphincteric reflex on rectal balloon inflation and the presence of marked rhythmic activity of the IAS and (2) the presence of ganglion cells and normal AChE activity in the rectal suction biopsy. And to make a correct diagnosis of IASA based on the criteria, one needs to understand and perform anorectal manometry and to understand anatomy of the terminal rectum.

41.3.3 ARM for Hirschprung's Disease and Idiopathic Constipation

Anorectal manometric study has been found to be useful in differentiating between two forms of megacolon, Hirschsprung's disease and idiopathic megacolon due to chronic constipation [4–7]. When a balloon placed in the rectum is inflated to stretch the rectal wall, there is normally a reflex relaxation of the internal anal sphincter. The absence of this rectosphincteric reflex suggests the failed reflex pathway and forms the basis of this simple and safe diagnostic test in Hirschsprung's disease, where ganglion cells, which are responsible for the reflex, are absent in the terminal rectum. In Hirschsprung's disease, there is no relaxation or there may even be paradoxical contraction of the internal anal sphincter. If sphincter relaxation is normal, Hirschsprung's disease can be reliably excluded as Jarvi et al. reported 100% negative predictive value [40].

On the other hand, patients with idiopathic constipation are expected to have rectosphincteric reflex as in normal subjects. Martelli et al. evaluated 1182 children complaining of constipation with or without encopresis by anorectal manometry, and all had a rectosphincteric reflex [41]. The systematic review by de Lorijn et al. revealed the sensitivity and specificity of ARM as a diagnostic test of Hirschsprung's disease (nine studies for a total of 400 patients) were 91% and 94%, respectively, and concluded age at which ARM was performed played no significant role with respect to sensitivity and specificity [42].

It has been suggested that false-negative test results of ARM for Hirschsprung's disease, which means positive rectosphincteric reflex in Hirschsprung's disease, can occur because of the displacement of the transducer probe or as a

consequence of relaxation of the external anal sphincter rather than the internal anal sphincter [5].

41.3.4 Reliability of ARM

Specificity of ARM as a diagnostic test of Hirschsprung's disease was calculated as 94% by a review of de Lorijn et al. [42], which means that even if the rectosphincteric reflex is not observed on ARM, one might not confirm Hirschsprung's disease histologically in a few cases examined. In fact, it may indicate the patient have other diseases than Hirschsprung's disease. However, when the rectosphincteric reflex is not detected by ARM, we need to pay careful attention to technical aspect of this meticulous study first of all.

It has been mentioned the commonest reason for failing to elicit the reflex is inflating the balloon before the anal canal has settled to a resting state. Overdistension will produce discomfort response which will mask the internal sphincter change. In a child with retentive behavior, there may be artifacts caused by voluntary contraction of the external anal sphincter and the gluteal muscles. Sedation, which does not interfere with the reflex, may be used when patients are young and restless. It has been stated that failure to elicit the reflex in non-Hirschsprung's disease cases was due to an inadequate stimulus to the rectum, the presence of feces alongside the probe making pressure changes, overstimulation producing a voluntary external sphincter contraction, or, most commonly, failure to wait for resting conditions to obtain [5–8, 39].

In the presence of a dilated rectum, it is necessary to inflate the balloon with large volume to elicit normal sphincter relaxation. Inadequate volume of air required to elicit the reflex is another common reason of failure. Vela and Rosenberg used up to 120 mL of balloon to feel resistance at the syringe [8].

Therefore, to say a patient does not have rectosphincteric reflex on ARM, we need to make sure the ARM is correctly performed with understanding of the pitfalls of techniques mentioned above (Table 41.1).

Table 41.1 Summary of the reported incidence data

Common reasons for failure of anorectal manometry
Failure to elicit the rectosphincteric reflex in normal subject
Failure to wait for resting conditions
Overdistension to produce discomfort response
Child with retentive behavior (voluntary contraction of the muscles)
Inadequate stimulus to the rectum
Presence of feces alongside the probe
False-negative test results of ARM for Hirschsprung's disease
Displacement of the transducer probe
Consequence of relaxation of the external anal sphincter rather than the internal anal sphincter

41.3.5 Anatomy of the Terminal Rectum

When a patient has a history of long-standing constipation since early period of life and has no relaxation of the internal anal sphincter, diagnosis for any disease should be confirmed with a rectal biopsy. If there is no ganglion cell found pathologically, you can diagnose the patient to have Hirschsprung's disease. When ganglion cells in the rectum are proven to be present, there has been dispute whether the patient can be diagnosed to have very short segment of aganglionosis, ultrashort segment Hirschsprung's disease, or not. That is because it has been considered to be difficult to determine whether the absence of the ganglion cells is physiological or not.

Aldridge and Campbell reported based on an autopsy study of 22 normal infants that there is "hypoganglionic" zone in the terminal rectum and it is found to extend an average of 4 mm in the myenteric plexus, 7 mm in the deep submucous plexus, and 10 mm in the superficial submucous plexus from and cranial to the anal valves or pectinate line of the anal canal [13]. In adult cadaver study, the mean distance of aganglionic bowel from the dentate line was 6.6 (range, 0–21) mm in Meissner's plexus and 5.1 (range, 0–15) mm in Auerbach's plexus. The normal distance of aganglionic bowel wall was stated to be 2 cm or less from the dentate line [43].

Several reports were published about the anatomical investigation on rectal biopsies. Ohi et al. analyzed the specimen obtained from 110 infants with abdominal distension and constipation and found the Meissner's ganglion cells were always present at the level of just above the dentate line of the rectum in the specimen of normal controls. They concluded that 5 mm oral to the dentate line was the most appropriate position of the rectal mucosal biopsy for the diagnosis of Hirschsprung's disease [44]. Taffazzoli et al. also reported the number of ganglia and ganglion cells of the submucous plexus decrease continuously toward the anus, but even the lowest segment is not aganglionic [45].

Review report of Gastro 2009 International Working Group on quantitative studies of cellular components of the enteric nervous system in the normal human gastrointestinal tract concluded that there is decrease of the density of myenteric ganglia in the rectum. The report also suggested effect of age on density of enteric neurons with significant age-related decrease [46].

41.3.6 Controversy on IASA

Proposed diagnostic criteria of the internal anal sphincter achalasia, also described as ultrashort Hirschsprung's disease, is the absence of rectosphincteric reflex with the presence of ganglion cells in the rectum. However, one should

cautiously make diagnosis of the disease based on the criteria after reviewing literatures and considering technical aspects of anorectal manometry with anatomical investigations on the terminal rectum.

Only after appropriate distention of the rectum by a balloon in a relaxed or sedated child with long-standing history of severe constipation could not demonstrate rectosphincteric reflex, Hirschsprung's disease and allied Hirschsprung's disease are suspected. Histologically, one may not be able to distinguish IASA from physiologically aganglionic or hypoganglionic terminal rectum by conventional hematoxylin and eosin staining alone [18, 19, 39]. Only when no nerve fibers with increased AChE activity are observed in the lamina propria, the disease of IASA can be diagnosed.

When IASA is diagnosed, we need to recognize that the entity may contain several unclarified pathogeneses of this condition. Although the incidence in the literature has been relatively high in children with prolonged constipation in some reports from Europe or the United States [22, 24], considering that very few cases are reported in a large cohort of Hirschsprung's disease and allied disorders in Japan [36, 47], the diagnostic criteria should be strictly observed.

It is noteworthy that Davidson and Bauer emphasized that all patients should first be treated conservatively but vigorously to determine whether they can have normal bowel movements. They recommended vigorous initial disimpaction by repeated enemas followed by relatively large doses of mineral oil as a therapeutic test. Only if there is a reaccumulation of the impaction in spite of the adequate administration of enemas and mineral oil should one be suspicious of some organic lesion. They concerned that their report might erroneously give any impression that many patients being managed for chronic constipation must suffer from this condition and must be studied by roentgenogram, motility technics, or operated upon [8]. This condition should be suspected after the therapy for chronic constipation is diligently carried out.

41.4 Treatment Aspect on Patients with IASA

There have been many reports when patients were diagnosed to be with sphincter achalasia, they were treated by internal sphincter myectomy followed by histological confirmation. Many authors who presented IASA patients performed sphincter myectomy and reported the outcomes of the procedure. Heikkinen et al. concluded that in the majority of patients with the disease can be treated, but in the long term, a significant number of patients suffer from soiling-related social problems [48], on the other hand, Doodnath and Puri reported the vast majority of IASA patients have normal bowel control following sphincter myectomy [49].

Other therapeutic option represented is botulinum toxin injection [50]. Consensus statement by an international working group about practical guide for primary enteric nervous system disorders says that botulinum toxin injection has been reported as a less invasive and efficacious tool and the response may serve as both a diagnostic and therapeutic tool. They recommend that if a decrease in anal sphincter pressure after the injection does not improve symptoms, it is unlikely that a myectomy would be curative [51].

However, a meta-analysis by Friedmacher and Puri indicates that in patients with IASA, posterior internal anal sphincter myectomy appears to be a more effective treatment option compared to intrasphincteric botulinum toxin injection. After injection, the rate of transient fecal incontinence, non-response, and subsequent surgical procedures was significantly higher compared to IAS myectomy [52].

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Chronic Idiopathic Intestinal Pseudo-Obstruction (CIIP)

42

Mitsuru Muto

42.1 Disease Concept

Intestinal pseudo-obstruction was first described in 1958 by Dudley et al. [1]. The reported case presented with serious ileus without mechanical obstruction. Faulk et al. proposed the term chronic intestinal pseudo-obstruction (CIPO) in 1978 [2]. CIPO is a functional motility disorder presenting with repetitive or continuous nonmechanical bowel obstructive symptoms, such as abdominal distension, nausea and vomiting, abdominal pain, and intestinal dilatation. Historically, CIPO in children has been variously referred to as chronic intestinal pseudo-obstruction (CIP), chronic intestinal pseudo-obstruction syndrome (CIPS or CIPOS), pseudo-Hirschsprung's disease, and chronic adynamic ileus [3–7]. This suggests that the epidemiological and clinical features of CIPO in children have been unclear.

CIPO is classified into three types: primary type, caused by gastrointestinal lesions; secondary type, associated with systemic illness or drugs; and "idiopathic" type with unknown etiology. CIPO is recognized as chronic idiopathic intestinal pseudo-obstruction (CIIP) when a conventional histological examination, such as hematoxylin and eosin staining, fails to show a meaningful pathology [3, 8].

As primary CIPO includes Hirschsprung's disease (aganglionosis) and allied Hirschsprung's diseases (except CIIP) (refer to other chapters), a diagnosis of childhood CIIP requires differentiation from these diseases. It is also important to differentiate secondary CIPO in the diagnosis of adult CIIP.

CIIP is characterized as a rare and intractable disease with an unknown etiology for which an effective treatment method has not yet been established [9]; high-quality evidence concerning its treatment is extremely lacking. This chapter mainly describes CIIP that develops in childhood based on a nationwide survey conducted in Japan and newly released clinical practice guidelines for allied Hirschsprung's disease by Tomoaki Taguchi's project group on research for "establishing guidelines for rare and intractable gastrointestinal diseases, spanning childhood to the transition phase." Supporting articles include journals in Japanese.

42.2 The Diagnosis

In this section, we will describe the diagnostic criteria for childhood CIIP newly established in Japan (Table 42.1).

The recognition of prolonged obstructive symptoms and exclusion of mechanical obstruction are key for the diagnosis of CIIP. The disease is considered to be "chronic" if the functional obstructive symptoms appear during the neonatal period and persist for the first 2 months of life or if it appears after the neonatal period and persists for longer than 6 months [3]. When no pathological abnormalities in the ganglion plexus of the affected intestine are exhibited, the disease is described as "idiopathic." "Pseudo-obstruction" denotes signs and symptoms resembling a physical obstruction to the luminal flow, including radiographic documentation of dilated bowel with air-fluid levels, in the absence of a true mechanical obstruction.

The duration of symptoms and the bowel obstructive conditions are determined from the clinical history and physical examination findings. The presence of intestinal dilatation, air-fluid level formation, and the absence of mechanical obstruction are confirmed by plain abdominal X-ray, computed tomography (CT), magnetic resonance imaging (MRI), or similar modalities [10, 11]. For neonates, radiological examinations in a standing or lateral decubitus position may be difficult, considering patient's condition, so the confirmation of air-fluid levels by plain abdominal X-ray is not necessarily required in neonatal cases. In the diagnosis of childhood CIIP, the location of dilated segments, the degree

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Table 42.1 Diagnostic criteria for chronic idiopathic intestinal pseudo-obstruction

The following seven items need to be satisfied:
1. Persistent or repetitive development over a long period of time of serious bowel obstructive symptoms that may require hospitalization, such as abdominal distension, nausea and vomiting, abdominal pain, etc.
2. Duration of symptoms is ≥2 months for neonatal onset and ≥6 months for onset in infancy or later
3. Gastrointestinal dilatation and air-fluid level noted on diagnostic imaging[a]
4. No lesions mechanically blocking the gastrointestinal tract
5. No pathological abnormalities in the nerve plexuses on HE staining obtained by an intestinal full-thickness biopsy[b]
6. Megacystis-microcolon-intestinal hypoperistalsis syndrome and segmental dilatation of intestine excluded
7. Secondary chronic intestinal pseudo-obstruction excluded[c]

[a]Confirmation of the air-fluid level on plain abdominal radiography in a standing position is not necessarily required for neonates.
[b]For adults, when an intestinal full-thickness biopsy is unobtainable, a characteristic peristalsis disorder should be confirmed by manometry or cine-MRI.
[c]Table 42.2 shows the secondary chronic intestinal pseudo-obstructions to be excluded.

of peristaltic disorder, and the presence of nonmechanical obstruction can be detected based on the gastrointestinal gas pattern on plain abdominal X-ray and gastrointestinal series. An intestinal full-thickness biopsy is indispensable for the definitive diagnosis of idiopathy and exclusion of other allied Hirschsprung's diseases, such as isolated hypoganglionosis and immaturity of ganglia [11, 12]. Its idiopathy is confirmed when conventional histological examination, such as hematoxylin and eosin staining, fails to show a meaningful pathology [8].

In adult cases of CIIP, it is important to differentiate true mechanical obstructions caused by neoplastic lesions, inflammation, and adhesion. In addition, the exclusion of secondary pseudo-obstructions is emphasized in the diagnosis of idiopathy. The secondary pseudo-obstructions to be differentiated are listed in Table 42.2. Generally, a full-thickness biopsy is not conducted in adult cases as it is for children. Cine-MRI and intestinal manometry are useful for assessing peristaltic disorders present in CIIP, and these two modalities are used instead of a full-thickness biopsy in adults [8, 13–15].

42.3 Clinical Manifestation

In February 2012, we conducted a nationwide survey in Japan for an assessment of epidemiological and clinical features of CIPO among children, involving facilities represented by members of the Japanese Society of Pediatric Surgeons; the Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition; and the Japanese Study Group of Pediatric Constipation [12]. A total of 92 responses were collected from 47 pediatric facilities, and 62 cases were diagnosed as pediatric CIPO. Considering the population of Japanese children younger than 15 years of age (16.7 million), the esti-

Table 42.2 Secondary chronic intestinal pseudo-obstruction

1. Gastrointestinal smooth muscle-related diseases
Systemic sclerosis
Dermatomyositis
Multiple myositis
Systemic lupus erythematosus
Mixed connective tissue disease (MCTD)
Ehlers-Danlos syndrome
Muscular dystrophy
Amyloidosis
Small bowel-based lymphoid infiltration
Brown bowel syndrome (Ceroidosis)
Mitochondrial encephalomyopathy
2. Gastrointestinal nerves-related diseases
Familial dysautonomia
Primary dysautonomia
Diabetic neuropathy
Myotonic dystrophy
Pseudo-obstruction after infection, such as EB virus, Herpes Zoster virus, and Rota virus
3. Endocrine diseases
Hypothyroidism
Hypoparathyroidism
Phaeochromocytoma
4. Metabolic diseases
Uremia
Porphyria
Serious electrolytes abnormality (K^+, Ca^{2+}, Mg^{2+})
5. Others
Celiac disease
Kawasaki disease
Eosinophilic enteritis
Paraneoplastic pseudo-obstruction
Mesenteric vein thrombosis
Side reactions to radiotherapy
Angioedema
Intestinal tuberculosis
Crohn's disease
Chagas disease
Paralytic ileus resulting from injury, after gastrointestinal surgery, intraperitoneal inflammation, etc.
Ogilvie syndrome
6. Drug-induced diseases
Antidepressant
Antianxiety drug
Anthraquinone-based laxative
Phenothiazine drugs
Vinca alkaloid
Anticholinergic drug
Opioid
Ca channel blocker
Verapamil

mated prevalence of pediatric CIPO was determined to be 3.7 per one million children. Pediatric CIPO therefore seems to be an extremely rare disease. Among these 62 cases, 49 (23 males, 26 females) met the diagnostic criteria of CIIP. The mean age of the patients was 12.1 years (median, 8 years; range, 0–43 years) at the time of the survey.

According to a previous nationwide survey conducted in the Japanese adult population, the number of patients with CIPO peaks at 40–50 years of age [16]. In contrast, in the pediatric population, CIPO as well as CIIP develops during the neonatal period in more than half of cases (Fig. 42.1).

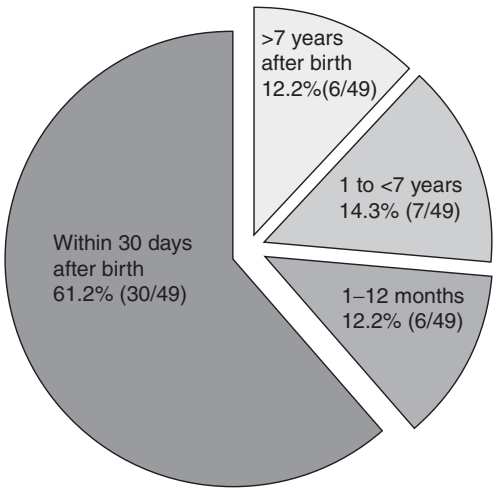

Fig. 42.1 Disease onset. More than 60% of patients developed CIIP in the neonatal period in Japan

Familial accumulation was noted in two families, and four female patients had familial incidence. A set of twins, both with megacystis (without presence of microcolon), developed CIIP during neonatal period, while two sisters, both with galactosemia, developed CIIP at school age.

The major initial symptoms are abdominal distension and vomiting for neonatal-onset cases and abdominal distension, vomiting, and chronic constipation for postneonatal-onset cases (Fig. 42.2). Peristalsis disorders may occur at single or multiple sites of the gastrointestinal tract. Dilated intestines are frequently observed in the small bowel and colon. In the majority of CIIP cases, remission and exacerbation of those pseudo-obstructive symptoms may be repeated with progressing conditions (Fig. 42.3). Repeated long-term hospitalization is therefore sometimes required. Oral intake was restricted in three-fourths of the CIIP patients, and more than half were dependent on parenteral nutrition in our former survey (Fig. 42.4).

We formulated severity criteria based on factors that impair the quality of a patient's daily life (Table 42.3). According to these criteria, 43 out of 49 (87.8%) CIIP children were assessed as severe cases.

CIIP is summarized as a rare, serious, and intractable disease.

42.4 Therapeutic Interventions

Treatment may start with conservative treatment, such as drug therapy and intravenous/enteral nutrition, and shift to invasive treatments, such as decompression by tubing or

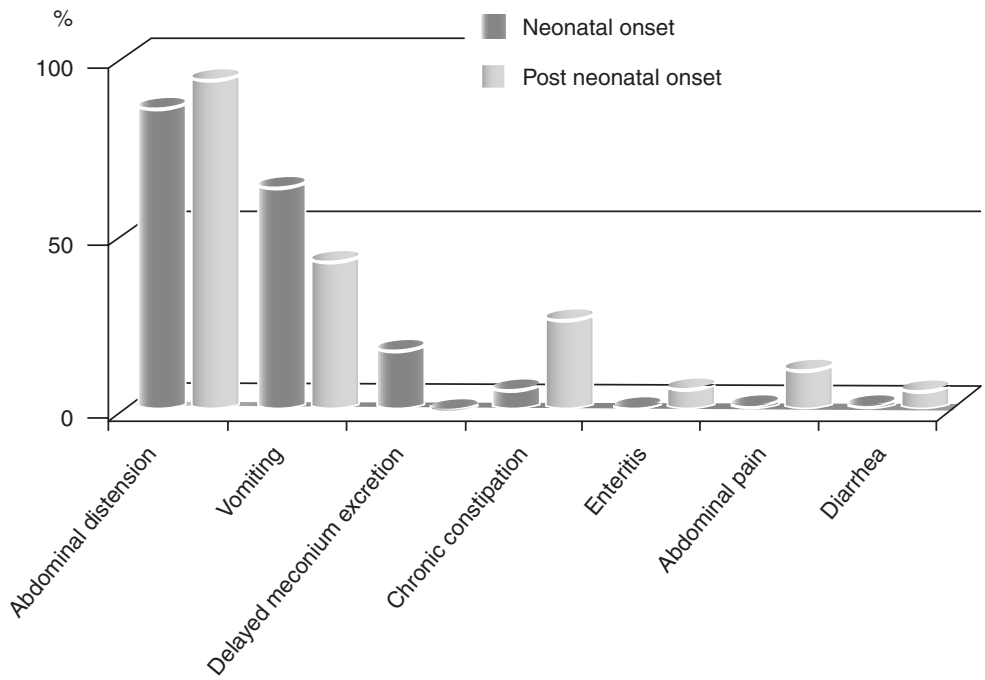

Fig. 42.2 Initial symptoms and signs (multiple answers allowed)

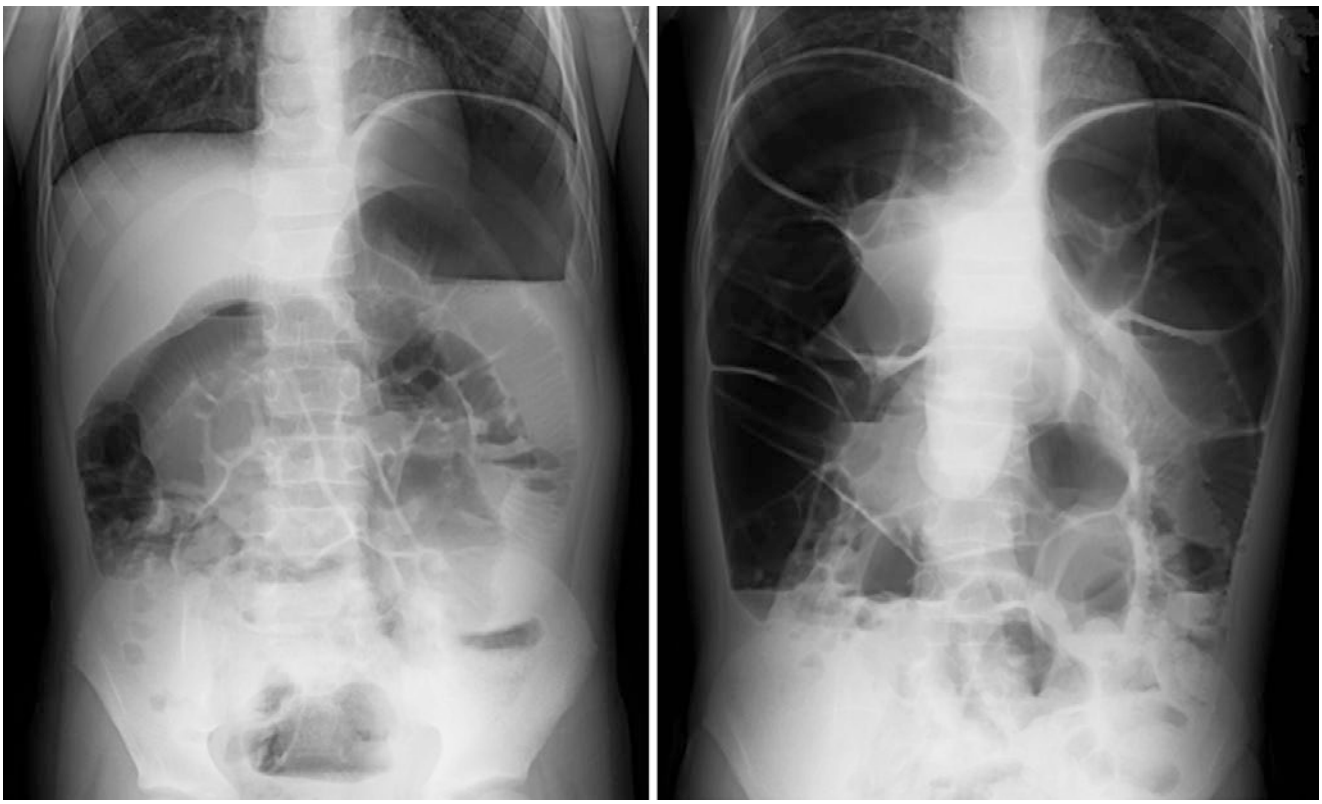

Fig. 42.3 Plain abdominal X-ray of a childhood with CIIP. At 7 years of age (left), intestinal dilatation and air-fluid were present. At 17 years of age (right), the dilatation had progressed, and free air was observed under the diaphragm

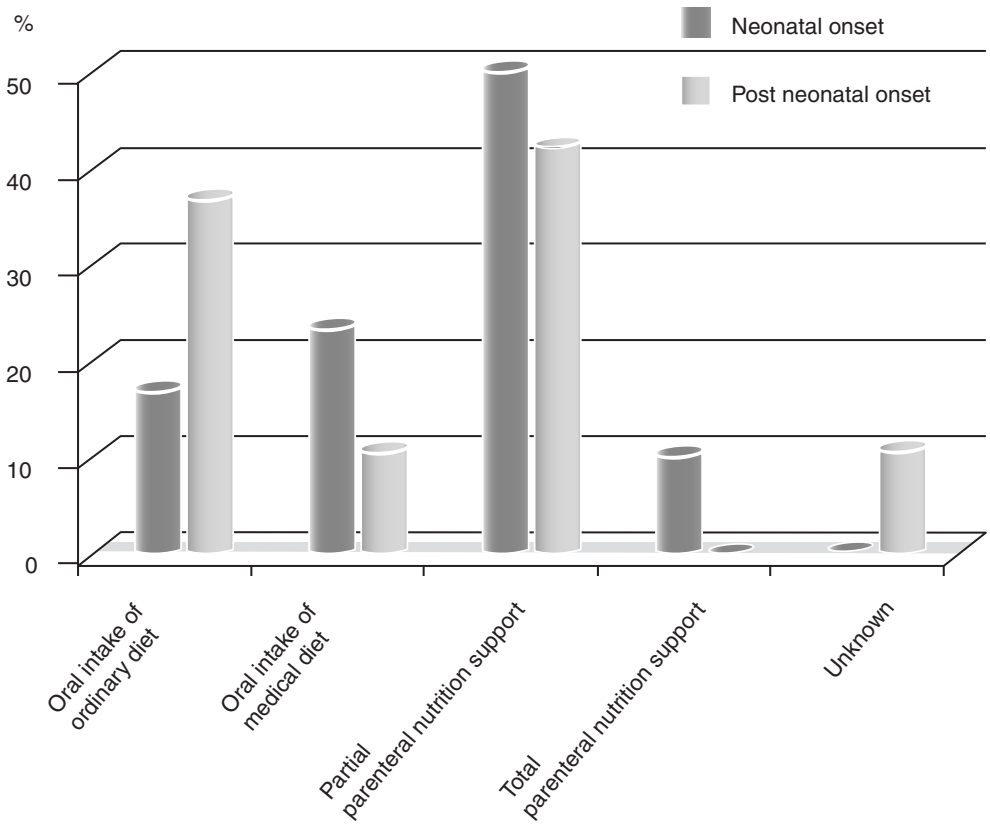

Fig. 42.4 Nutritional management. Only a quarter (24.5%; 12/49) of the patients were receiving a normal oral diet independent of any nutritional support. Half (53.1%; 26/49) of the patients depended on parenteral nutritional support

Table 42.3 Severity criteria

Severe case is defined as one whose daily life is significantly impaired due to bowel obstructive symptoms, such as abdominal distension, nausea and vomiting, and abdominal pain, and when at least one of the following three items is met:
1. Parenteral nutrition is required
2. Enteral nutrition is required
3. Continuous gastrointestinal decompression is required[a]

[a]Gastrointestinal decompression refers to the drainage of intestinal contents through enterostomy, gastrostomy, nasogastric tube, ileus tube, transanal tube, etc.

enterostomy, as the condition progresses. However, no treatment modality has been clearly shown to be effective in relieving symptoms.

42.4.1 Drug Therapy

Some drugs are used to control CIIP, including prokinetic agents, Chinese medicine (dai-kenchu-tou), probiotics, antibiotics, laxatives, and antidiarrheals. However, few randomized control trials (RCTs) or case series have provided supporting evidence, and the available articles are mostly case reports. There are no recommended medications [17].

Attempts have been made to improve pseudo-obstructive symptoms with prokinetic agents; one case series examined the efficacy of prucalopride [11], and one cross-sectional study examined the efficacy of cisapride [18]. Some case reports have suggested the usefulness of cisapride, the administration of which resulted in an increased intake of enteral nutrients and a reduction in the intestinal transit time [19–21]. However, other case reports have found this agent to be ineffective [22–24]. The effectiveness of mosapride for CIIP has not yet been reported.

Two case reports have described the usefulness of dai-kenchu-tou, a Chinese medicine, in improving gastrointestinal motility and bowel obstructive symptoms [25, 26]; however, one case report conversely found it to be ineffective [27].

Two case reports have described an increased intake of enteral nutrition and reduced incidence of enteritis treating with probiotics [28, 29]. No adverse events associated with probiotics have been reported, but evidence supporting its effectiveness is not sufficient.

Erythromycin is sometimes administered to enhance intestinal motility, and some case reports have shown its effects on increasing the enteral nutrition intake [27, 30]. One case report described the improvement of pseudo-obstruction with polymyxin B [31]. No adverse events have been reported with the administration of antibiotics for CIIP, but evidence supporting their efficacy is lacking at present.

Regarding other drugs, one case report found laxatives to be effective [20], and two case reports found that prostaglandin improved bowel obstructive symptoms [31, 32]. Again, however, the effectiveness of those agents remains unclear. Buprenorphine, a weak opioid, was reported as an agent for relieving abdominal pain [14]. Although the evidence is not sufficient, buprenorphine may be useful for relieving symptoms of abdominal pain associated with CIIP.

42.4.2 Nutritional Therapy

CIIP is a disease that requires repeated, prolonged fasting and central venous nutrition management due to enteritis caused by stagnation of intestinal contents. Advances in the management of optimal parenteral/enteral nutrition support may prolong the survival of patients [14, 33].

Since CIIP may have a long duration of symptoms, special attention needs to be paid to the life-threatening complications related to long-term parenteral nutrition, such as trace element deficiency, electrolyte disturbance, parenteral nutrition-associated liver disease (PNALD), and catheter-related blood stream infections (CRBSIs). Of the 49 cases in our survey, 18 (36.7%) had PNALD, and CRBSIs were seen in 10 (20.4%).

Semi-digested nutrients, the concomitant use of semi-digested nutrients and a low-residue diet, and digestive nutrients are reported to be useful for enteral nutrition in patients with a functional ileus [21]. However, enteral nutrition may not be able to be administered in cases with aggravated symptoms. Further investigation into what kinds of enteral nutrients are most useful is needed.

42.4.3 Gastrointestinal Decompression

Appropriate gastrointestinal decompression should be considered on a case-by-case basis. Intermittent decompression via enteric tube may be effective in some CIIP cases, and enterostomy may be effective in other cases. Gastrointestinal decompression may enable enteral feeding and encourage growth and long-term survival. In our nationwide survey, decompression of the dilated tracts was performed in 39 CIIP children (79.6%, 39/49), 28 of whom (71.8%, 28/39) had permanent enterostomas. Of these 28 cases, five (17.9%) were able to receive oral intake of an ordinary diet.

Nasogastric tube decompression for CIIP has been reported to be effective in the short term. Regarding the nature of CIIP, once the bowel pseudo-obstruction symptoms subside, they may relapse again [34]. The placement of an ileus tube may improve abdominal distension and abdominal pain remarkably, but its long-term efficacy is not clear [35]. There have been some cases in which oral intake was enabled by intestinal lavage and continuous decompression through enterostomy [36]. Antegrade continence enema may be sug-

gested to improve defecation and abdominal distension [26]. Although temporary efficacy has been reported with both jejunostomy and ileostomy, colonostomy has not been shown to be effective in any cases and has conversely been reported not to have improved bowel obstruction symptoms at all [37]. No side effects or adverse events accompanying decompression therapy have been reported.

42.4.4 Radical Surgical Treatment

When gastrointestinal decompression is not effective, the risk of intestinal perforation or enteritis should be kept in mind. Unfortunately, however, even if the dilated segments are resected, obstructive symptoms may relapse due to dysfunction in the remaining intestine. Intestinal resection is not believed to improve the pseudo-obstructive symptoms. Avoiding multiple surgery is recommended in the treatment of CIIP [9, 16].

In cases of duodenal dilatation, duodenojejunostomy is suggested to improve the intestinal transit of the dilated segment. It may relieve the pseudo-obstructive symptoms to some extent [38].

In our nationwide survey, 13 out of 49 patients (26.5%) underwent intestinal resection. However, less than one-quarter (3/13, 23.1%) were able to receive oral intake of an ordinary diet; the rest continued to depend on parenteral nutrition or required enteral nutrition with a medical diet. A tendency toward undergoing multiple surgeries was seen in the group treated with intestinal resection compared with the group treated without intestinal resection (average number of surgical interventions: 3.85 times vs. 2.33 times, $p = 0.047$). Attempts to improve pseudo-obstruction by resection of the dilated intestine, including ileocecal resection and colectomy, failed in several studies [24, 30, 39]. No reports have shown the efficacy of intestinal resection with clear evidence.

42.4.5 Small Bowel Transplantation

Small bowel transplantation may be indicated as a final measure when conservative treatments become ineffective due to complications, when patients have suffered from intolerable pain for a long period of time, or when repeated catheter-related infections lead to the loss of central venous access and progression of hepatopathy. Since CIIP is often characterized by disorder of gastric emptying, the impaired native gastric outlet function needs to be considered when small bowel transplantation is planned and performed.

Multivisceral transplantation is generally performed [40, 41], and isolated small bowel transplantation plus partial gastrectomy with graft-gastric or graft-duodenal anastomoses may be another option [42].

In Japan, isolated small bowel transplantation for CIIP has been performed in three cases. In two of these cases, two anastomoses were performed at the oral side to add graft-duodenal or graft-jejunal anastomosis to graft-gastric anastomosis. In both cases, however, oral intake was not easily established. Only one out of the three cases has survived.

42.5 The Prognosis of Chronic Idiopathic Intestinal Pseudo-Obstruction

An estimated 10–25% children with CIPO died before adulthood in the past quarter century [4, 5]. Advances in the management of intestinal failure, including optimal nutrition support and improvements in the management of sepsis, may prolong the survival of CIIP patients. In our survey in Japan, only three children with CIIP died from enteritis or sepsis, resulting in a survival rate of 93.9% (46/49). The number of cases transitioning from childhood to adult is likely to increase in the future [12].

In clinical practice, repeated hospitalization is sometimes required for patients with CIIP due to exacerbation of pseudo-obstructive symptoms. Even for outpatient cases, the requirement of intravenous nutrition support and enterostomy itself may significantly limit patients' daily life. While the prognosis of CIIP with respect to the survival is good, this outcome is deemed unsatisfactory given the restriction of patients' long-term quality of daily life [43].

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Segmental Dilatation of the Intestine

43

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43.1 Introduction

Segmental dilatation of the intestine (SD) is a rare lesion defined as limited bowel dilatation with a three- to fourfold increase in size with an abrupt transition between the normal and dilated bowel and no intrinsic or extrinsic barrier distal to the dilatation. It was first described in 1959 by Swenson and Rathauser [1] as "a new entity," which is distinct from Hirschsprung's disease in terms of the pathological findings of normal ganglion cells. Since then, over 100 cases have been reported in the world literature; however the etiology remains difficult to determine, and the clinical features have not been established.

The first and most recent retrospective cohort study on allied disorder of Hirschsprung's disease (ADHD) was performed in Japan. ADHD was classified into two categories depending on the pathological findings of ganglion cells: (a) abnormal ganglia, including immaturity of ganglia, hypoganglionosis, and isolated intestinal neuronal dysplasia, and (b) normal ganglia, including megacystis-microcolon-intestinal hypoperistalsis syndrome, internal anal sphincter achalasia, chronic idiopathic pseudoobstruction, and SD [2]. All cases diagnosed with SD in Japanese authorized institutions in study period were collected and analyzed. And the first retrospective cohort study about SD was reported in 2015 [3].

43.2 Etiology

The etiology of SD remains unknown. Some of the hypotheses that have been proposed are the following:

(a) Abnormal tortuous vessels which were noted by Rossi and Komi [4, 5] in their cases might be the cause of this condition, because the presence of the anomalous artery, whether the cause or effect of the dilatation, suggested that the situation was of congenital origin.
(b) Ueda suggested that vascular insufficiency during intussusceptions resulting in hypoplasia of the intestinal muscle could be the cause of SD [6]; however, Heller rejected Ueda's theory by pointing out that the dilated segments were found to be hypertrophic rather than hypotrophic in the majority of the cases [7].
(c) Heller suggested that SD was a malformation sharing a mutual pathogenic complex with congenital cysts, diverticula, and duplications [7]. The occurrence of heterotopic tissues seen in the area of dilated segment supports this theory.
(d) Volvulus and kinking due to a long mesentery during the embryologic period were also suggested causes of SD [8].
(e) Marsden stated that interruption of the continuity of the nerve fibers and the nerve plexus in islands of ectopic tissue could be an etiologic factor [9, 10].
(f) Irving reported that in cases with omphalocele, the intestinal segment in the omphalocele sac entrapped, constricted, and partially obstructed at both ends was the cause of SD. The adhesion of the segment to the sac could be either the cause or the result of the entrapment of the loop [11].
(g) Irving also postulated that even if there was no omphalocele, strangulation of the intestine in the umbilical ring during the early stage of development (prior to involution) was the cause of SD.

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43.3 The Clinical Features and Diagnosis

From the reviews of 73 cases [3, 12–45], 53 pediatric cases (72.6%) are discovered in neonatal periods. And the first retrospective cohort study in Japan also showed that the most common onset period was neonatal in 18 of 28 cases (64.3%) including seven cases diagnosed prenatally. SD is localized mainly in the ileum and colon, occasionally in the jejunum, and exceptionally the duodenum (Fig. 43.1). More than half of the described cases were neonatal discoveries presented with symptoms of intestinal obstruction in which the clinical picture was hard to differentiate from more common causes of occlusion as intestinal atresia, Hirschsprung's disease, meconium ileus, and midgut volvulus [12]. Consequently, they had a diagnosis of this condition during the neonatal period. In older infants and children, symptoms vary. Chronic constipation, anemia, and abdominal pain are also encountered in older infants (Table 43.1). Gastrointestinal bleeding and anemia are found because of ulceration of the dilated segment that is more profuse in the presence of heterotopic gastric mucosa [13, 14]. Occasionally, concurrent malformation such as intestinal malformation, omphalocele, and congenital heart disease were found [2]. From the review of the literature and the retrospective cohort study in Japan, concurrent malformation was found

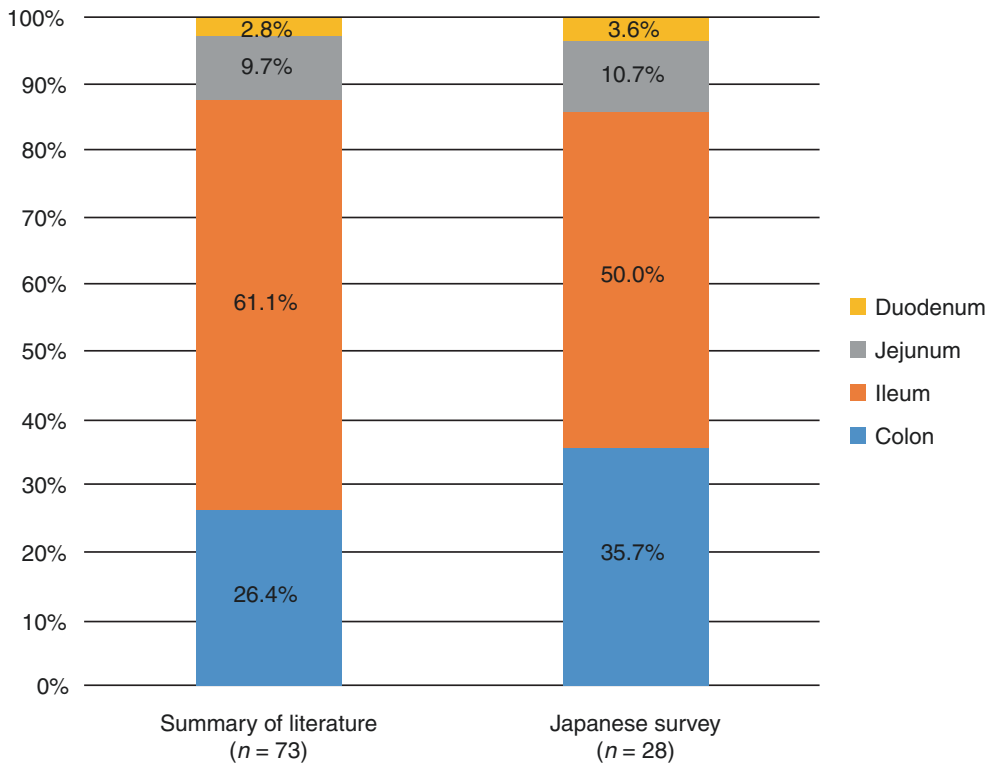

Fig. 43.1 Segment of dilatation. Segmental dilatation is localized mainly in the ileum and colon, occasionally in the jejunum, and exceptionally the duodenum

Table 43.1 Symptoms

		Summary of literature	Japanese survey
		(*n* = 53)	(*n* = 18)
Neonatal period	Abdominal distention	32 cases (60.4%)	13 cases (72.2%)
	Vomiting	19 cases (35.8%)	10 cases (55.6%)
	Fetal intra-abdominal cyst	15 cases (28.3%)	7 cases (38.9%)
	Omphalocele	7 cases (13.2%)	–
	Delayed passage ofmeconium	4 cases (7.5%)	4 cases (22.2%)
		(*n* = 20)	(*n* = 10)
After neonatal period	Abdominal distention	11 cases (55%)	7 cases (70%)
	Vomiting	7 cases (35%)	4 cases (40%)
	Chronic constipation	7 cases (35%)	6 cases (60%)
	Anemia	4 cases (20%)	Lease (10%)
	Abdominal pain	3 cases (15%)	–
	Enteritis	2 cases (10%)	2 cases (10%)

in 33 of 73 cases (45.2%) and 10 of 28 cases (35.7%), respectively.

Because the symptom is not specific and the definitive diagnosis is difficult, SD is usually diagnosed incidentally during surgery. However, the anomaly can also be suspected or diagnosed preoperatively on the basis of radiologic findings [15, 16]. The classic feature of SD on plain radiographs is the marked segmental dilatation of the bowel loop, with or without an air-fluid level (Fig. 43.2). Abdominal computed tomography (CT) may help to diagnose the SD characterized by a dilated tubular or cystic structure communicating with adjacent bowel loops through narrow transition points [17]. Contrast enema studies are often useful for confirming segmental dilatation of the bowel loop [16].

43.4 Criteria

The criteria for diagnosis of this entity, as proposed by Swenson and Rathauser, are as follows [1]: (a) limited bowel dilatation with a three- to fourfold increase in size, (b) an abrupt transition between the dilated and normal bowel, (c) no intrinsic or extrinsic barrier distal to the dilatation, (d) clinical picture of intestinal occlusion or subocclusion, (e) normality of the neuronal plexus, and (f) complete recovery after resection of the affected segment.

The diagnosis of definitive SD occurred when all criteria were met and the possible SD was diagnosed solely based on anatomical features (a–c) without occlusive findings (Fig. 43.3), surgery of histological examination.

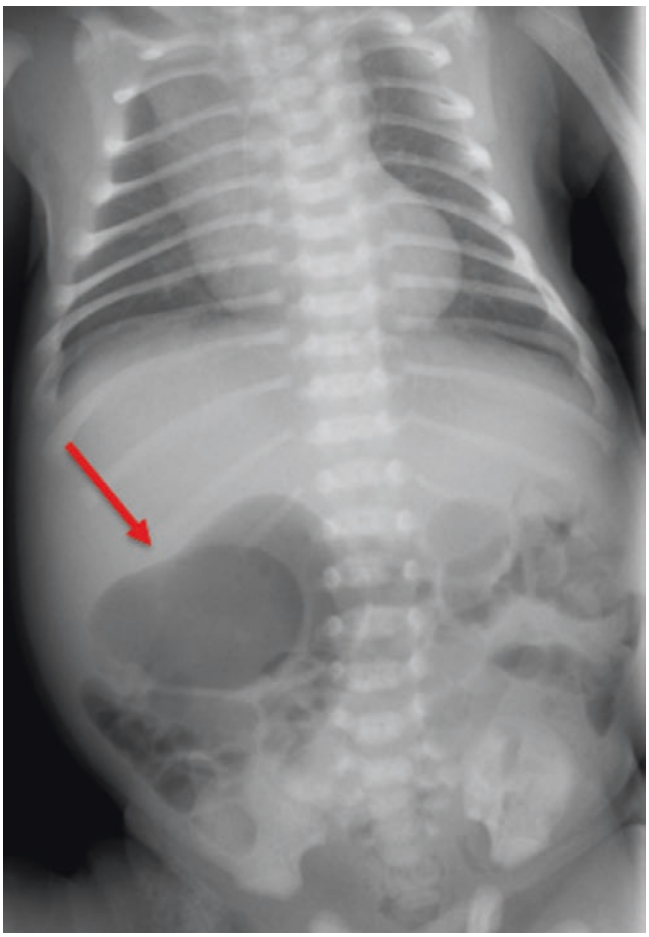

Fig. 43.2 X-ray in supine position. This X-ray showed a dilated bowel (arrow) in the right side of the abdomen

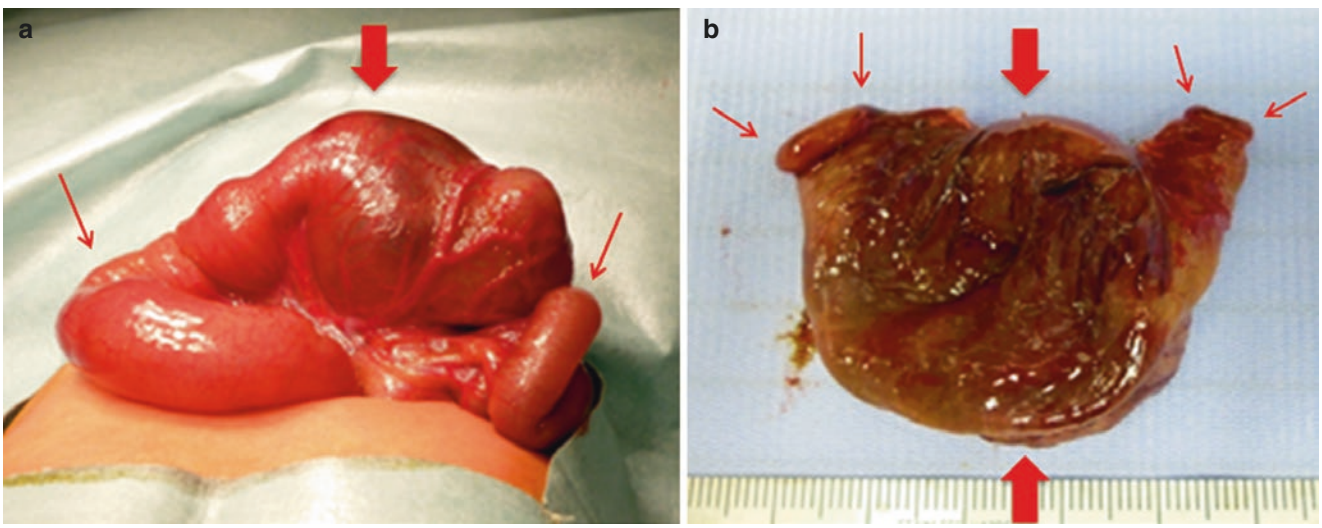

Fig. 43.3 (**a**) Intraoperative finding. (**b**) Resected specimen. Locally dilated ileum with an abrupt transition between the dilated and normal bowel. No intrinsic or extrinsic barrier distal to the dilatation. Thick arrow indicates dilated bowel and thin arrow indicates normal bowel

43.5 Pathology

The histopathological findings are the most important diagnostic criteria. The presence of normal ganglion cells in number and morphology is a major factor for differential diagnosis [18]. However, some of the cases showed hypertrophied or very thin muscle layer in the involved segment in histopathological evaluation [19]. Heterotopic gastric or pancreatic tissue is also reported in dilated intestinal segment [13, 17, 20] (Table 43.2). However, all resected segments show normal presence of ganglion cells in myenteric and submucosal plexuses. In a recent study, the dislocation of the myenteric plexus within the circular muscle layer was reported [21] (Fig. 43.4).

Table 43.2 Histological findings

		Summary of literature ($n = 73$)	Japanese survey ($n = 28$)
Abnormal muscle layer	Thickening	12 cases (16.4%)	1 case (3.6%)
	Thinning	8 cases (11.0%)	2 cases (7.1%)
Ectopic tissue	Gastric	6 cases (8.2%)	Lease (3.6%)
	Pancreatic	3 cases (4.1%)	Lease (3.6%)

The immunohistological investigation for SD was done in only five reports [19, 22–25]. They used S-100, Ret, or MAP5 for neural marker and c-kit for mesenchymal marker. As a result of the immunohistological investigation of SD, three reports identified the disorder of interstitial cells of Cajal (ICCs) [23–25], and two reports concluded the pathogenesis of local myopathy [19, 22]. ICCs have been ascribed as the pacemaker cells that coordinate peristaltic behavior, and the loss or decrease of ICCs has been implicated in several disorders of human intestinal motility [46]. ICCs were immunohistochemically identified using an antibody for c-kit. Three reports indicated that the pathogenesis of SD was the local absence of ICCs. On the other hand, two reports indicated the pathogenesis was local myopathy. Known muscle markers are useless to detect the myopathy, and fibrosis or vacuolization of HE staining is the sign that demonstrates the myopathy [47]. The different pathological findings from myopathy to disorder of ICCs suggest that there might be different types of SD. Precise histological and immunohistological investigations in future cases of SD might provide more detailed information about its etiology.

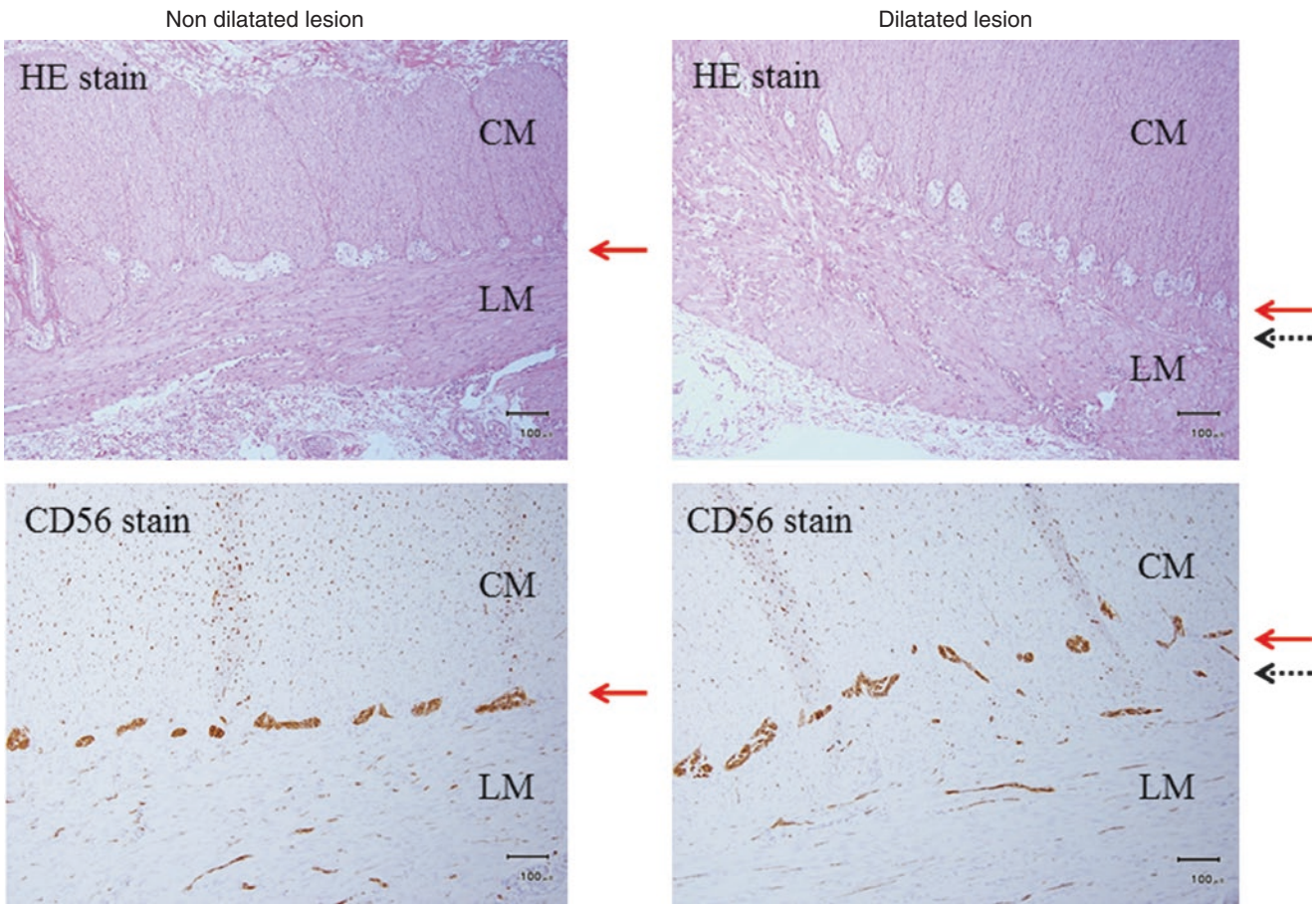

Fig. 43.4 Pathological findings. Myenteric plexus shifts to the circular muscle layer (red arrow) at the dilatated lesion, but not at the nondilatated lesion. Dotted arrow indicates intermuscular layer. *CM* circular muscle layer, *LM* longitudinal muscle layer

43.6 Treatment

The treatment of SD depends on the clinical condition of the patient, the presentation, the surgeon's experience in dealing with such malformations, and the association with other malformations. The definitive surgery is resection of the involved segment and end-to-end anastomosis with/without proximal colostomy [17]. In the case of patients who are critically ill (such as patients with perforation or chromosomal abnormalities), an ileostomy can be fashioned without excision of the segmental dilatation [26]. In the case with anorectal malformations, colostomy is recommended for anorectoplasty in the second stage. A covering ileostomy can be also fashioned due to the presence of multiple colonic anastomoses [26].

Some reports recommend the use of laparoscopic procedure in the surgical treatment of SD. Laparoscopy was found to be a reliable diagnostic tool and is a minimally invasive procedure that provides safe and superior cosmetic results [13].

According to the retrospective cohort study in Japan [3] that the details were clear, surgical resection of dilated intestine was performed in 27 of 28 cases. Enterostomy was also performed in four cases and gastrostomy in two cases. One case was waiting for operation at the time of the surveys.

43.7 Prognosis

Most patients who underwent surgery for SD showed an uncomplicated postoperative course. The survival rate is excellent unless other serious complications or anomalies are present. In the retrospective cohort study [2], all of the patients survived.

43.8 Conclusion and Future Directions

Segmental dilatation of the intestine is a rare malformation with an unknown etiology and a misleading clinical presentation. From the review of 73 cases and the first cohort study in Japan [3], most of the clinical features have been revealed, but the etiology of SD remains unclear. In some cases, immunohistological investigations are useful for diagnosis. Precise histological and immunohistological investigations in future cases of SD might provide more detailed information about its etiology. The treatment is simple and the postoperative course is usually uneventful.

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The Future Consideration in Allied Disorders of Hirschsprung's Disease

44

Shigeru Ono

The allied disorders of Hirschsprung's disease (ADHDs) are characterized by functional intestinal obstruction that clinically resembles Hirschsprung's disease despite the presence of ganglion cells in the rectum [1]. They can be divided into conditions with abnormal ganglia, such as immaturity of ganglia (IG), hypoganglionosis (HG), and intestinal neuronal dysplasia (IND), and conditions with normal ganglia, such as megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS), segmental dilatation (SD), internal anal sphincter achalasia (IASA), and chronic idiopathic intestinal pseudo-obstruction (CIIP) [2]. This classification of ADHDs may be reasonable and has been widely accepted in Japan. However, Puri et al. proposed a slightly different classification of these disorders, called variants of Hirschsprung's disease in 2012 [3]. Variations in pathological characteristics and morbidity affect the clinical course and prognosis. All studies and discussions about ADHDs should be based on the same classification system with incorporation of pathological findings. International collaboration in data collection and classification of ADHDs is required to understand the clinical characteristics, reduce mortality, and improve clinical outcomes.

In Japan, nationwide surveys about ADHDs were performed only in 1988 and 1993 [4]. Precise data on patients with ADHD has been limited. In 2014, the Japanese Study Group of Allied Disorders of Hirschsprung's Disease attempted to collect data on all cases of ADHD from 2001 to 2010 in Japan [2]. Based on this survey, the incidence and clinical outcomes of these conditions have been revealed gradually [2]. Moreover, it is revealed that congenital HG, MMIHS, and CIIP have poorer prognosis than IG, IND, SD, and IASA.

Of these seven known ADHDs, three conditions (isolated HG, MMIHS, and CIIP) were officially certified as intractable diseases by the Ministry of Health, Labour and Welfare of Japan in 2016. Therefore, it became very important and pressing to establish diagnostic criteria and appropriate treatment strategies for ADHD, especially HG, MMIHS, and CIIP. The other four conditions (IG, IND, SD, and IASA) have a good clinical course and are extremely rare; thus, these diseases are unlikely to cause confusion when making therapeutic decisions in clinical practice.

In 2017, pathological diagnosis and severity criteria were defined for the seven known allied Hirschsprung's diseases in clinical practice guidelines [5]. It may be a milestone for the clinical aspects in diagnosis and treatment of ADHD. Clinical practice guidelines for this group of diseases have not been drafted before. Therefore, this guideline is anticipated to be helpful for decision-making in diagnosis and treatment at each institution in Japan. In this clinical practice guideline for ADHD, seven clinical questions (CQs) were developed for the three intractable diseases (HG, MMIHS, and CIIP). They included diagnosis, drug therapy, gastrointestinal decompression, nutritional therapy, radical surgical treatment, small bowel transplantation, and prognosis. These CQs with wide clinical application are surely useful in clinical practice from a clinician's point of view.

It is also essential to clarify prognostic factors for each type of ADHD. Because HG, MMIHS, and CIIP may contain some cases with a severe clinical course or poor prognosis, appropriate treatment strategies including the type and timing for surgery and postoperative management should be established.

Congenital HG is considered to have a poorer prognosis than other ADHDs with abnormal ganglia. Thus, early diagnosis and appropriate treatment are important. For isolated HG, immunohistochemical staining for Hu/CD and CD56 has the potential to make a definitive histopathological diagnosis [6]. It may be also useful to distinguish congenital from acquired isolated HG. It goes without saying that further collection and analysis of precise data of isolated HG are important. Moreover, further pathological study using the combination of several immunostaining techniques may help identify prognostic factors for HG.

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On another front, the extreme low incidence of ADHDs is one of the reasons of dilemma in treatment strategy and poor prognosis of these diseases. The mean number of cases per institution was only 3.7 cases, and more than half of the institution had three cases or fewer [2]. ADHDs are rare disorders in neonates and infants, so the intensification of suspicious cases of ADHD to the specified institutions may contribute to improved clinical course and prognosis. Moreover, because of the rarity of the disorder and range of morbidity, specialized treatment strategies for each patient may be required.

In the near future, severe cases of HG, MMIHS, and CIIP can be cured with organ transplantation. According to the Intestinal Transplant Registry, small bowel transplantation was performed in 2600 cases or more by 2011 all over the world. Among them, patients with motility disorder as primary disease accounted for 19% of children. In Japan, only 26 transplantations in 23 cases were performed by 2014. The postoperative patient survival and graft survival rates at 1 years, 5 years, and 10 years are 87%, 68%, and 58% and 80%, 59%, and 44%, respectively. The short-term results are relatively good, but the long-term prognosis is still poor [7].

From the data of small bowel transplantation cases for HG in Japan as of January 2016 based on a report from the Japanese Intestinal Transplantation Registry, nine small bowel transplantations (living donors, six; brain-dead donors, three) in eight cases have been performed, and the patient survival rate was 88%, and the graft survival rate was 56%. While there are certain advantages from bowel transplantation, such as achieving successful oral intake and reduced dependency on parenteral nutrition, acute and chronic rejection may result in graft removal in many cases. Therefore, we should carefully and strictly determine the indications of small bowel transplantation as a surgical treatment for IHG. It is emphasized that the control using the patient's own intestine is a priority.

Small bowel transplantation for MMIHS has never been performed in Japan (as of January 2016). Most of the cases reported in the literature are multiple organ transplantations including the stomach, small bowel, colon, liver, pancreas, and kidney, as hepatic failure and renal failure are accompanied at the time of transplantation in the majority of reported cases [8]. The patient and graft survival rates after small bowel transplantation are poor in the long term. However, considering the extremely poor prognosis of MMIHS and the difficulties of combined liver and small bowel transplantation in Japan, isolated small bowel transplantation has the potential of being useful for MMIHS when the disease is not complicated with hepatic failure.

Treatment strategy for CIIPs may start with conservative treatments, such as drug therapy and intravenous and enteral nutrition, and then shift to invasive treatments, such as decompression by tubing or enterostomy, as the condition progresses. In the cases in which the disease is refractory despite these treatments, and in which the disease is complicated by a lack of central venous access or repeated episodes of sepsis, small bowel transplantation may be performed as a final measure. Since this disease is often characterized by disorder of gastric emptying, multiple organ transplantation including the stomach has been generally performed overseas [9]. In Japan, small bowel transplantation for CIIP has been performed in three cases. However, oral intake was not easily established, and only one of the three cases has survived. CIIP is an intractable disease with an unknown etiology for which an effective treatment method has not yet been established. Small bowel transplantation may be the only therapy for severe cases, but the oral intake is not easily established after transplantation. As for the current situation regarding small bowel transplantation for CIIP in Japan, multiple organ transplantation is not feasible. Isolated small bowel transplantation should be provided carefully with close consideration of the appropriate anastomosis approach for ensuring the gastric emptying function in each case of CIIPs.

At any rate future studies should examine the appropriateness of small bowel transplantation versus multiple organ transplantation for such patients with severe prognosis of ADHD.

Another important problem regarding ADHDs is about so-called transition. Since almost all diseases in ADHDs develop in childhood, only clinical practice for pediatric patients has been focused and developed. However, an increasing number of patients are enjoying long-term survival due to recent progress in management and treatment strategies. Therefore, clinical practice during the transitional period from childhood to adulthood also needs to be considered hereafter.

From the point of view of making revision of clinical practice guidelines for ADHDs, further collection of precise clinical data on all suspected cases in Japan and close follow-up survey of all cases are required. A central pathological diagnostic system is also needed and is expected to be very helpful in making accurate diagnoses for all participating institutions.

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Transition in the Patients with Hirschsprung's Disease

45

Minoru Yagi and Suguru Fukahori

45.1 Introduction

Pediatric surgery is a specialized field of surgery, and remarkable progress in this field has been made in Japan by pediatric surgeons in cooperation with neonatologists, anesthesiologists, nursing staff, and so on. Neonatal surgery first started in European countries and the United States before the Second World War. Conversely, the level of pediatric surgery in the 1950s in Japan was far behind that observed in Western countries. The Japanese Society of Pediatric Surgeons was established in 1964. In 2013, the society celebrated its 50-year anniversary after its commencement.

Nowadays, the achievement of successful outcomes in this group of complicated patients (neonatal surgical diseases, biliary atresia, pediatric malignant tumors, and so on) appears to be changed from lifesaving to long-term survival. Therefore, the long-term survivors in Japan usually require a special treatment and multidisciplinary management by pediatric surgeons in cooperation with otolaryngologists, urologists, gynecologists, and general physicians. Therefore, it is necessary to manage transition. In this condition, transition is defined as serving as an intermediary from the pediatric (surgical) field to the adult clinical department for follow-up including multidisciplinary medical management in the long term.

However, what kind of clinical department of doctors follows up postoperative patients aged over 20 years old with pediatric surgical field disease? This issue is crucial as the transitional problem arises when such patients reach the adolescent age. In case of onset of malignant tumor and adult-aged disease, it is difficult to manage by the pediatric surgeon. On the other hand, doctors of adult clinical departments are not familiar with intractable and rare diseases in the pediatric surgical field. Therefore, it is difficult for them to respond to requests in comprehensive medical managements including primary disease except emergency support.

In this chapter, outline of the long-term result and several underlining problems of Hirschsprung's disease (HD) 20 years after birth are described.

45.2 Historical Development of the Operative Procedure in HD

The operative management of HD has evolved dramatically, from full-thickness rectosigmoid dissection by Swenson [1], an endorectal dissection by Soave [2], a retrorectal pouch procedure by Duhamel [3], and a low anterior resection by Rehbein [4] to more recently a primary repair [5, 6] that can be done transanally [7], by using laparoscopic techniques [8]. Removal of the aganglionic bowel, pulling through the ganglionic bowel, and preserving the anal canal and sphincter mechanism remain as the principles to surgical repair of HD regardless of technique. Long-term results after operative management vary given the differences in the surgery performed, the age of treatment, the involved aganglionic segment, the amount of colon resected, and the patient's and parent's perception of fecal continence [7, 9]. Functional problems after a pull-through, including enterocolitis, constipation, and fecal incontinence, clearly occur, but the true incidence of each complication is unclear, and their definitions vary widely. Pediatric surgeons recognize that these sequelae can have considerable effects on children's well-being as well as their physical, emotional, and social development [9]. Understanding the technical differences between the different HD operations is the key to evaluating any postoperative problems the patients may experience [10].

Considering such circumstances, the mainstream operative method in HD is transanal endorectal pull-through; its postoperative anorectal motor function is almost excellent. However, there were many kinds of operative procedures, and complications such as fecal incontinence, accident, constipation, and urinary disturbance were often identified in the postoperative patients with previous procedures except transanal

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endorectal pull-through in the short and long term. Consequently, it is essential to perform long-term follow-up including urological treatments [11]. Furthermore, it is necessary to discuss the pros and cons of transition in the long term in postoperative patients with HD aged above 20 years old.

45.3 Classification

There are two types of transition in the patients with HD above 20 years old. One is complete transition to adult clinical departments. The other is partial transition to exclusive related adult clinical departments through the original pediatric surgical department.

45.4 Current State of Transition

Limited circle of the postoperative patients with previous procedures except transanal endorectal pull-through is subject to transfer to transition in the short and long term. Most of the type of HD that requires transition is generally long or extensive type, in addition to complicated cases regardless of length of aganglionic segments.

In the postoperative patients with HD aged above 20 years old, there are patients who require some kinds of complicated management methods in long or extensive type. Fecal incontinence, accident, constipation, bloating with gas, and urinary disturbance were often identified in these patients. Also, the patient with ischemic changed colon was reported as the severe post-operative complication. This case is finally transferred to the construction of an artificial anus [12]. Under the attending pediatric surgeon, it is necessary to manage strict defecational control and financial support including counseling and public medical financial support in the intractable cases.

Considering such circumstances, complete transition to adult clinical departments is often difficult. Most of the successful transitions are partial transition to exclusive related adult clinical departments from the original pediatric surgical department to relieve the workload and to improve quality in the medical service using the Hirschsprung's disease summary sheet for transition as is shown in Table 45.1.

Table 45.1 Hirschsprung's disease summary for transition

Name Birth date Gestational age Guardian name Guardian address Gurdian telephone No.	weeks days	Gender Age Birth weight Relationship	years months g		
Diagnosis					
Type of aganglionic area	Ultra-short, short (rectosigmoid), long (descending, transverse, ascending), total, extending (ileal, jejunal)				
Operation	**Operative procedures**	**Operation date**	**Name of Hospital**		
1 2 3 4 5					
Current status of management					
Oral intake	(yes, no)				
Tube feeding	(yes, no)				
Total parenteral nutrition	(yes, no)				
Stoma	(yes, no)				
Constructed portion of Stoma					
Drugs	Everyday medicine	(yes, no)	Name of drug	Usage	Dosage
Emergency response	Symptom to be possible to occur	Hospital to respond	Clinical department to respond	Name of doctor to respond	Telephone no.
1 2 3 4					
Medical expense support		(yes, no)			
Certificate of impairment grading		(yes, no)			

Transition is not easy, not to mention the complicated cases regardless of length of aganglionic segments.

In Japan, there is a very close relationship, which is called "Kizuna," between the patients and the attending surgeon. The patients and their families tend not to desire to leave from the attending surgeons. This distinctive relationship is one of the major obstacles that interrupt the transition process.

45.5 New Attempt in Solution of Transitional Problems

To resolve the transitional problems, Taguchi et al. [13] proposed the establishment of a medical complex-type center based on the combination of hospital and transition center (Fig. 45.1). This system means that children hospital connects to general hospital on-site. Furthermore, the clinical problems can be resolved without putting off time after gathering some kinds of medical departments and multidisciplinary staff members through this center.

The medical departments involve actually surgery, internal medicine, urology, gynecology, orthopedic surgery, plastic surgery, otolaryngology, psychiatry, digestive tract surgery, hepatobiliary pancreatic surgery, and transplantation surgery. Multidisciplinary staff members involve WOC (wound, ostomy, and continence) specialized nurse, physiotherapist, clinical psychologist, and so on. Medical complex centers in which children hospital and general hospital are in parallel are developed, and several transition outpatient clinics are beginning to operate in Japan.

In this manner, transition has taken the first step in this way but is still in the middle of the road. There are still many kinds of problems (system of specified medical service fees, arrangement of checking up at the hospital, and so on) to be resolved. In the pediatric surgical field, the following diseases are the main objects for transition: anorectal malformation, HD (limited cases), allied disorder of HD, intestinal failure, spina bifida, biliary atresia, choledochal cyst, pediatric lymphatic malformation, malignant tumor, and so on.

45.6 Conclusions

There are some cases wherein it is difficult to understand the pathophysiology of pediatric surgical disease, to perform decision-making in the choice of medical modality, and to transfer from pediatric surgery to adult medical department. It is an important effort to improve quality in the medical service and to relieve the workload by discussing matters about transition to be solved by patients and medical staff as well as management of chronic disease by pediatrician.

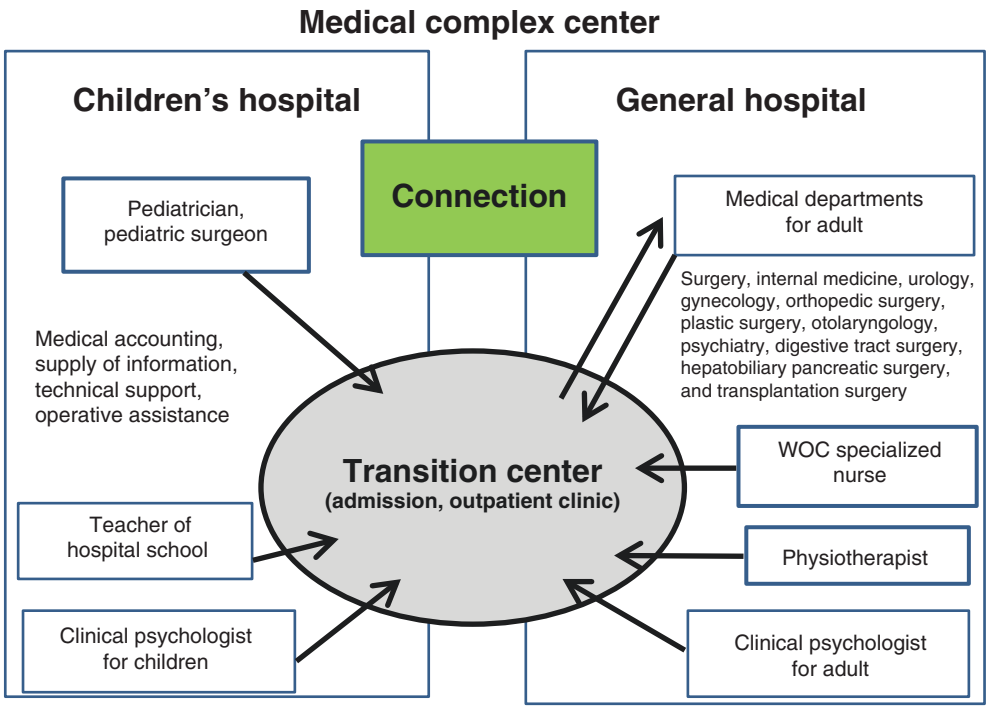

Fig. 45.1 Medical complex center

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Health-Care Transition for Patients with Allied Disorders of Hirschsprung's Disease

46

Hideki Soh

46.1 Health-Care Transitions

Recently due to advances in pediatric, medical, and surgical care, many children with severe disease have survived to adulthood. On the other hand, the number of the patient who continues to need medical care for refractory chronic disease or complications even in adolescent or adulthood has increased [1]. Such patients are called young adult with special health-care needs (YASHCN).

Along with the maturity of individuals' personalities, it is expected that the relationship between patients and health-care system will change from protective care under their parents and pediatrician to autonomous medical care under self-determination.

Most young people with special care needs should be able to find their way into and negotiate through adult systems of care [2]. However, many adolescents and young adults with severe medical conditions and disabilities that limit their ability to function and result in complicating social, emotional, or behavioral sequelae experience difficulty transitioning from child to adult health care [3, 4].

For these patients to receive appropriate medical care in accordance with age-related changes in physical condition, complications, and physical and personality maturity, the transitions in health care for individual patients from childhood care to adult appropriate health care should be established.

46.2 Health-Care Transitions for Patients with Allied Disorders of Hirschsprung's Disease

Allied disorders of Hirschsprung's disease (ADHD), such as isolated hypoganglionosis, chronic intestinal pseudo-obstruction, and megacystis microcolon intestinal hypoperistalsis syndrome, have been proposed to be the concept of the functional obstruction of the intestine with the presence of ganglion cells in the terminal rectum [5].

It is known that this rare and refractory disease develops in the neonatal period and follows a chronic course. Currently, there is no specific treatment for this condition. Chronic intestinal hypoperistalsis will be sustained for a long time, and intestinal obstruction symptom is prolonged in patients with severe symptom. Enteritis repeats and becomes more severe in some case. The intestines are often dilated chronically, so in a few cases, the dilated bowel twists and strangles. In these cases establishing oral feeding and enteral nutrition is difficult, and total parenteral nutrition is required for long term. And some patients receive an enterostomy for decompressing the bowel [6–8].

In recent years, the progress of nutrition management and the understanding of pathophysiology of ADHD have gradually improved the prognosis. However, even in long-term survival cases, sustained special cares are still required. As these patients grow from childhood to adolescence or adulthood, the health-care transitions are getting more important.

However, because ADHD is a very rare condition despite the necessity of lifelong medical care, the understanding about the pathology, physiology, treatment, and care of this disease may not be sufficient among most health-care providers. This rarity of disease and complexity of care are suspected to be one factor impeding spreading health-care transitions of ADHD.

Actually, symptomatic and palliative cares may play a key role in ADHD care, including intestinal decompression and nutritional support, including long-term PN currently. Because home parenteral nutrition (HPN) is almost established at adult health-care field also, it is considered that there are not so many problems about the health-care transitions in this respect. Meanwhile, it is needed to meticulously control abdominal symptom due to intestinal peristalsis disorder, such as abdominal distension, vomiting, abdominal pain, and recurrent enteritis. Additionally, it is also necessary to discuss the indication of small bowel or

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multivisceral transplantation in some severe cases of this condition. So sufficient understanding of this condition and care is necessary for medical stuff.

Based on this, it is not so easy to transition to an adult health-care system, so it is realistic to continue medical care based on pediatric medical systems while strongly linking adult health-care systems.

Specific care in ADHD in adolescent and adulthood is as follows. In cases where abdominal and nutritional condition is relatively good, introduction of HPN enables enrollment and work. About the management of HPN, it is almost the same as management of diseases causing adult intestinal failure such as other short bowel syndrome. It is important to prevent complications associated with parenteral nutrition such as catheter-related blood stream infection and liver dysfunction. In case with high degree of dependence on HPN, it may be difficult to work extremely heavily on the body, work in the outdoors for a long time in a hot day, and work over a long period of restraint time. It is desirable to work at appropriate room temperature in a situation that allows to supply water, electrolyte, and nutrient frequently. Depending on severity, intestinal decompression, enteral nutrition, and PN are needed permanently; it should be paid sufficient attention to prevent catheter infection and to preserve venous access.

On the other hand, as abdominal symptoms vary, special knowledge is required. Continuous decompression of the gastrointestinal tract is necessary, and it is important to strongly recommend cooperation with the adult health-care system and pediatric medical care team where some experience is accumulated.

Moreover, it is a group of diseases whose treatment should be seamlessly continued from childhood to adulthood, and it is necessary to prepare programs including seamless diagnostic criteria, severity classification, guidelines, education, and guidance of medical procedures.

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