World Journal of Pediatric Surgery

Conditions that mimic Hirschsprung's disease, but that are not Hirschsprung's disease

Shun Onishi , Satoshi Ieiri

To cite: Onishi S, Ieiri S. Conditions that mimic Hirschsprung's disease, but that are not Hirschsprung's disease. *World J Pediatr Surg* 2025;**8**:e000918. doi:10.1136/wjps-2024-000918

Received 28 August 2024
Accepted 14 January 2025

ABSTRACT

Hirschsprung's disease (HSCR) is widely recognized in pediatric surgery. This condition has been elucidated, and therapeutic approaches have been developed. However, even when ganglion cells are present in the rectum, some patients still experience symptoms such as bowel obstruction, intestinal dilatation, and chronic constipation, which are similar to those observed in HSCR. A consensus regarding the terminology for these diseases is yet to be established. This group of diseases was defined as 'allied disorders of Hirschsprung's disease' (ADHD). They are classified into two categories based on pathology: (1) Abnormal ganglia, including immaturity of ganglia, hypoganglionosis, and intestinal neuronal dysplasia; and (2) Normal ganglia, including megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS), segmental dilatation, internal anal sphincter achalasia, and chronic idiopathic intestinal pseudo-obstruction (CIIP). Hypoganglionosis, MMIHS, and CIIP are particularly severe and not curable by surgery. Guidelines were compiled to facilitate an accurate clinical diagnosis and provide appropriate treatment strategies for each disease. A full-thickness rectal biopsy with H&E and acetylcholinesterase staining is often required for a differential diagnosis. Patients are now able to survive longer with enteral nutrition combined with long-term intravenous nutrition and decompression of the gastrointestinal tract. However, all treatment strategies are symptomatic. It is necessary to improve the results of small intestine transplantation and to develop new therapies using regenerative medicine.

INTRODUCTION

Hirschsprung's disease (HSCR) is widely recognized in pediatric surgery. This condition has been elucidated, and therapeutic approaches have been developed. In clinical and research settings, there is a disease group with symptoms and laboratory findings similar to those of HSCR, despite the presence of ganglion cells in the rectum. In Japan, it has been called 'Allied disorders of Hirschsprung's disease (ADHD)' (ADHD). ADHD is generally classified pathologically into abnormal and normal ganglion cells. However, ADHD is currently difficult to diagnose and treat because it is a mixture of intractable and spontaneously resolving disorders with no established diagnostic criteria.

Several nationwide surveys have been performed, and clinical guidelines have been developed based on these data.[1 2] We review here the definitions of ADHD and the specifics of each disorder.

This review presents the results of a nationwide survey on ADHD in Japan and introduces recent findings. Our aim is to provide a comprehensive understanding to improve diagnosis, treatment, and support for individuals with ADHD.

DEFINITION OF ALLIED DISORDERS OF HIRSCHSPRUNG'S DISEASE

The term ADHD refers to a group of diseases characterized by symptoms and signs similar to those of HSCR, such as chronic constipation, bowel obstruction, and intestinal dilatation, despite the presence of ganglionic cells in the rectum. Ravitch first described this condition as 'pseudo HSCR' in the *Annals of Surgery* in 1958.[3] Since then, various terminologies have been used, including HSCR-related disorders, variant HSCR, Allied disorder-HSCR (AD-HSCR), pseudo-HSCR, and HSCR-related neuromuscular disorders of the intestine.[4 5]

In Japan, this entity is generally referred to as ADHD.[2 6] Healthcare specialists in this disease group, including pediatric surgeons, pediatricians, pathologists, and adult physicians, have repeatedly discussed the disease concept and classification.[7] The seven diseases were defined as ADHD (box 1). They are classified into two categories based on pathology by hematoxylin and eosin (H&E) and acetylcholinesterase (AchE) staining: (1) Abnormal ganglia, including immaturity of ganglia (IG), isolated hypoganglionosis (IHG), and intestinal neuronal dysplasia (IND); (2) Normal ganglia, including megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS), segmental dilatation, internal anal

Department of Pediatric Surgery, Kagoshima University Graduate School of Medicine and Dental Sciences, Kagoshima, Kagoshima, Japan

Correspondence to
Dr Satoshi Ieiri; sieiri@m.kufm.kagoshima-u.ac.jp

Box 1 Classification of allied disorders of Hirschsprung's disease

Diseases with intestinal ganglion cell abnormality
1. Immaturity of ganglia
2. Isolated hypoganglionosis
3. Intestinal neuronal dysplasia

Diseases without intestinal ganglion cell abnormality (H&E or acetylcholinesterase staining)
4. Megacystis microcolon intestinal hypoperistalsis syndrome
5. Segmental dilatation of intestine
6. Internal anal sphincter achalasia
7. Chronic idiopathic intestinal pseudo-obstruction

sphincter achalasia (IASA), and chronic idiopathic intestinal pseudo-obstruction (CIIP). IG, congenital hypoganglionosis, MMIHS, and CIIP are involved in the intestinal tract, that is, these conditions affect long segments of the intestinal tract. IND, acquired hypoganglionosis, IASA, and segmental dilatation are considered to be localized lesions. IG, MMIHS, and CIIP are particularly severe and not curable by surgery.

PATHOPHYSIOLOGY AND TREATMENT

Patients with ADHD often present with lower gastrointestinal obstruction symptoms such as abdominal distention and bilious vomiting from the neonatal period. Patients with congenital hypoganglionosis or MMIHS exhibit neonatal ileus, which must be differentiated from small intestine-type HSCR or ileal obstruction. In infancy and later, persistent and severe constipation and abdominal distention may be the primary complaints leading to the diagnosis. Patients with CIIP experience recurrent episodes of symptom relief and exacerbation.

In congenital hypoganglionosis, MMIHS, and CIIP, the affected intestinal tract is extensive, and patients experience persistent or recurrent intestinal obstruction symptoms. The prognosis is poor because patients may die from sepsis caused by small intestinal bacterial overgrowth due to intestinal immobility or liver failure resulting from the hepatic burden of prolonged high-calorie intravenous infusion.[8]

Treatment includes: (1) Enema, bowel lavage, placement of a decompression tube, and decompression of the gastrointestinal tract by stoma or tube enterostomy; (2) Parenteral nutritional management with a central venous catheter; and (3) Resection of the immobile dilated intestinal tract. However, all treatment strategies are symptomatic.

DIAGNOSTIC METHOD

Diagnosis is usually made by rectal mucosal biopsy (RMB). RMB provides a larger and deeper biopsy compared with a standard endoscopic forceps biopsy. RMB is usually adequate for obtaining a sufficient submucosal specimen for a diagnosis. Frozen sections stained with H&E plus AChE enzyme histochemistry and H&E-stained paraffin-embedded sections should be used as standard techniques for diagnosing HSCR in rectal biopsies from children.[9]

The diagnostic benefits of calretinin were reported by several papers, and many institutions use calretinin staining. Calretinin is normally present in the cytoplasm and nerve processes of a subset of enteric ganglion cells. In the aganglionic segment of HSCR, calretinin immunoreactivity in the muscularis mucosae and superficial submucosa is lost.[10] The European Paediatric Surgeons' Association reported that the most-used histological and immunostaining methods were H&E staining (77%), AChE staining (74%), and calretinin staining (31%)[11] in 2017. The sensitivity and specificity of calretinin staining are reported to range from 96.49% to 100% and 99.1% to 100%, respectively, which are slightly lower than the values for AChE staining.[12 13] AChE-positive fibers are difficult to diagnose with AChE staining in the neonatal period since they are not increased. Some reports suggest that calretinin staining contributes to early diagnosis because calretinin can be stained even soon after birth.[14 15] The choice of immunostaining such as calretinin or AChE staining in addition to H&E staining is currently dependent on the preference of the facility and specialist.

When therapy-resistant constipation or functional bowel obstruction is continuously present, although the presence of ganglion cells and normal AchE activity is confirmed by RMB, a full-thickness rectal biopsy is required for a differential diagnosis. Intestinal specimens with a longitudinal length of 10 mm and a short axis of 5 mm are obtained. Immunohistochemistry is a beneficial and good diagnostic adjunct to be replaced by enzyme histochemistry to delineate the immature neurons (B-cell/CLL lymphoma 2: 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 (smooth muscle actin: SMA).[2] Immunolocalization of the RNA-binding protein 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.[16]

IMMATURITY OF GANGLIA

At the 24th Congress of the Japanese Association of Pediatric Surgeons in 1987, Okamoto *et al.* presented ADHD as the main theme, reporting results from a nationwide survey.[17] In these reports, IG was characterized by a normal number of ganglion cells in the intestinal wall but with extreme immaturity. Subsequently, from 1991 to 1993, a more detailed survey was conducted under the project 'Clinicopathological studies on the diagnosis, treatment, and pathogenesis of pseudo-HSCR and

related disorders', funded by the Japan Society for the Promotion of Science.

The assumed representative clinical features of IG are as follows: (1) Ileus symptoms from the neonatal period, (2) Normal AchE activity, (3) Microcolon to small colon is shown in the findings of the rectum, (4) The rectoanal inhibitory reflex evaluated by an anorectal manometry test is often negative in the neonatal period, but the test becomes normal in infancy, (5) The intestinal tract often resembles that of meconium disease, (6) The lesions extend into the small intestine, (7) Defecation is usually obtained with an ileal stoma, and (8) After a few months, the neuronal cells mature and the stoma can be closed, showing a good prognosis.[18 19]

Pathological findings included a normally sized Auerbach's plexus, normal or slightly increased number of ganglion cells, smaller nuclei, and fewer enteric ganglia. A palisading-like pattern was confirmed at the time of the initial ileostomy (median age, 2.5 days), and the palisading-like pattern completely disappeared by the time of stoma closure (median age, 215 days) in all 10 cases registered in a nationwide survey in Japan.[20] A palisading-like pattern has not been observed in other diseases.

According to a nationwide survey in Japan, there were 28 cases of IG among the 353 cases of ADHD. Twenty-three cases required an ileal stoma, and the stoma could be closed in 17 patients. All 28 patients survived, and 25 patients were on a normal diet, 3 were on a polymeric formula, 2 were on an elemental diet, and 2 were on parenteral nutrition.

ISOLATED HYPOGANGLIONOSIS

IHG is a congenital gastrointestinal disorder with a poor prognosis that causes severe functional bowel obstruction during the neonatal period. Most patients require long-term life-sustaining enterostomy and parenteral nutrition, and in severe cases, small-bowel transplantation may be indicated.

Diagnosis criteria are: (1) Bowel obstruction symptoms present in the early neonatal period and (2) The intestinal nerve plexus is hypoplastic and the number of ganglion cells is significantly less than normal on a pathological examination. A severe case is defined as one in which daily life is significantly impaired due to bowel obstruction symptoms, such as abdominal distension, nausea, vomiting, and abdominal pain. Additionally, at least one of the following three criteria must be met: (1) Parenteral nutrition is required, (2) Enteral nutrition is required, and (3) Continuous gastrointestinal decompression is required.[7]

IHG is the most challenging disease for ADHD. This difficulty arises because the concept of the primary disease remains unclear, and a definitive diagnostic method has not been clearly established. Differentiating IHG from HSCR using barium enema or rectoanal manometry is particularly challenging (figure 1). While a whole-mount

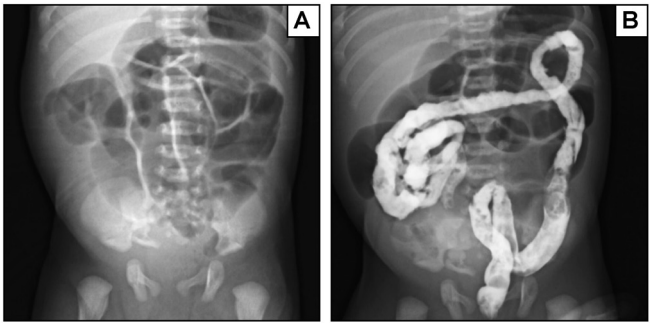

Figure 1 Abdominal X-ray and barium enema in isolated hypoganglionosis examinations at 11 days of birth. (A) Abdominal X-ray shows intestinal dilatation. (B) Barium enema shows microcolon due to obstruction.

preparation of the neural plexus is preferable for morphological observation of the myenteric plexus (Auerbach's plexus), the diagnosis of IHG has primarily relied on detecting a reduced number of neurocytes in the plexus. Numerous studies have demonstrated the efficacy of full-thickness gastrointestinal biopsies, especially from the small and large bowels, in diagnosing IHG.[21] When assessing neurocyte distribution via H&E staining proves challenging, various histochemical staining techniques can aid in the diagnosis. These include AChE, HuC/HuD antibody, nicotinamide adenine dinucleotide phosphate, succinate dehydrogenase, lactate dehydrogenase, and silver staining. A significant indicator of IHG is the presence of ≤20 HuC/HuD-positive cells per centimeter in the muscularis propria of a resected intestinal specimen, which is notably lower than that in the normal intestinal tissue. HuC/HuD staining is particularly useful for identifying decreases in ganglion cells. Patients with IHG typically exhibit small-intestinal nerve plexuses and a low number of ganglion cells. While individual ganglion cells are small during the neonatal period and grow as the patient matures, their numbers remain constant. In IHG, the number of HuC/HuD-positive cells is significantly reduced, making this staining method a crucial pathological finding for the accurate and prompt diagnosis of the condition[22] (figure 2).

The primary treatment strategy is to perform nutritional management using parenteral nutrition with a central venous catheter and enteral nutrition while adding appropriate decompression surgery to prevent enteritis caused by retention. An enterostomy is essential for decompression. Currently, based on the available evidence, there are no effective therapeutic agents that can be recommended to ameliorate gastrointestinal dysfunction and symptoms associated with IHG. A nationwide survey from 2001 to 2010 showed that patients who underwent initial jejunostomy had a better prognosis than those who underwent ileostomy. For successful management, patients should undergo jejunostomy at <50 cm from the ligament of Treitz during the neonatal period.[23] Stoma type may also affect the patient prognosis. Yamada *et al.* evaluated 19 patients and concluded

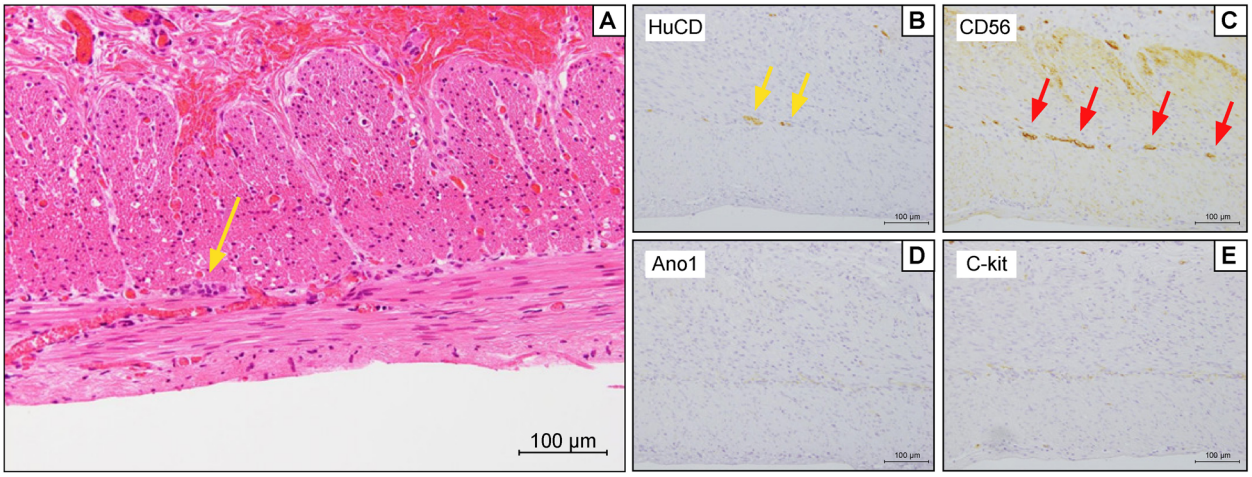

Figure 2 Pathological findings of isolated hypoganglionosis. Jejunostomy was created, and biopsy was performed on the seventeenth day after birth. Biopsy specimens from the ileum. (A) H&E staining. A small ganglion cell was obtained in the Auerbach plexus. (B) HuCD immunostaining. A small number of immature and tiny cells are observed (yellow arrows). (C) CD56 immunostaining. A small number of immature and tiny cells in the Auerbach plexus are observed (red arrows). (D) Ano1 immunostaining. A small number of Cajal cells in the Auerbach plexus. (E) c-kit immunostaining. A small number of Cajal cells in the Auerbach plexus.

that patients with Santulli-type or Bishop-Koop-type stomas had better body mass indexes and less parenteral nutrition dependency in terms of volume than those with end-stomas or tube-stomas.[24] The need for resection of the dysfunctional intestine on the anorectal side of the jejunostomy can be inferred from the pilot study results; however, no cohort study has been conducted. In severe cases, small-bowel transplantation or multiorgan transplantation may be indicated, but the prognosis for these treatments is still developing.

According to a nationwide survey in Japan, the 10-year survival rate of patients with IHG was 78% (70/90 patients).[25] Multidisciplinary treatment significantly improved the survival rate from 12.6% in 1977 to 55.6% in 2011. Patients who received appropriate therapy could expect prolonged survival. Among these cases, some patients achieved disease control with oral intake alone, demonstrated average growth or only mild growth impairment, and were able to attend school. However, in many cases, long-term nutritional support and enterostomy remained necessary.

INTESTINAL NEURONAL DYSPLASIA

Fadda *et al.* further separated IND into two distinct subtypes, based on clinical and histological conditions: IND type A and IND type B.[26] Type A IND is very rare, accounting for less than 5% of cases. Type B is the majority of IND cases. IND type A is characterized by congenital aplasia or hypoplasia of the sympathetic innervation. Patients with IND type A typically present in the neonatal period with abnormal distension, bowel obstruction, and episodes of diarrhea with hemorrhagic stool. In contrast, IND type B is characterized by hyperplasia of the parasympathetic plexus.[27 28]

IND was first described by Meier-Ruge in 1971 in children with clinical symptoms resembling HSCR.[29] IND is characterized by hyperplasia of the submucosal plexus, resulting in clinical manifestations that resemble HSCR, despite distinct histological differences. It is reported that IND is detected independently or as isolated IND in 0.3%–62% of all suction rectal biopsies worldwide.[30] IND can also occur in conjunction with other gastrointestinal neuropathies. When IND coexists with another gastrointestinal disorder, this condition is referred to as associated IND. IND is typically associated with HSCR, with reported incidence rates ranging from 20% to 66%.[31]

Several reports have described the histology of IND, and as a result, the typical histological findings have been established as hyperganglionosis, giant ganglia, ectopic ganglion cells, and increased AChE activity in the lamina propria and around the submucosal vessels.[32] These findings may exist independently, in association with anal atresia, or in the ganglionated bowel proximal to the aganglionic segment of patients with HSCR. Whether these pathological findings are due to congenital changes, secondary changes related to growth and development, or constipation, remains controversial.

Conservative therapy, such as laxatives and enemas, can often manage IND-related conditions. If these symptoms do not improve with conservative treatment, internal anal sphincter myotomy or myectomy may be considered. In rare cases, bowel resection may be necessary. Due to the lack of standard diagnostic criteria and pathological surveillance strategies, reports of morbidity tend to vary among centers. Uniform diagnostic criteria and practical methodologies are essential to address this issue and must be shared among centers.[28]

MEGACYSTIS MICROCOLON INTESTINAL HYPOPERISTALSIS SYNDROME

MMIHS is a severe disease that presents with intestinal obstruction-like symptoms in the neonatal period and subsequently leads to intestinal failure, accompanied by megacolon and a small colon. Many of these cases require gastrointestinal decompression via gastrostomy or intestinal stoma in the neonatal period. Pathological examination reveals no abnormalities in the enteric plexus.

A gastrointestinal series is recommended for cases presenting with symptoms of bowel obstruction, such as abdominal distension and vomiting, during the neonatal period when no organic obstruction is observed. When microcolon is observed and megalocystis is simultaneously confirmed by cystography, CT, or ultrasonography, MMIHS is strongly suspected. An intestinal full-thickness biopsy is recommended for a definitive diagnosis to differentiate it from other forms of ADHD.[1] Cystography can be helpful for clearly diagnosing megalocystis, but this modality cannot provide further clinical information. Enemas are useful for confirming the presence of microcolon, which is an indispensable sign of this disease.

Laparotomy is often performed during the neonatal period in many cases due to severe abdominal distension. A full-thickness intestinal biopsy is necessary during laparotomy to differentiate MMIHS from other types of ADHD. The absence of ganglion cell abnormalities is characteristic of MMIHS.

Due to intestinal failure, parenteral or enteral nutrition must be used for a long time. A nationwide survey from 2001 to 2010 enrolled 19 definitive and 5 suspected cases.[33] An enterostomy was performed to provide decompression in 16 of the 19 definitive cases.[1] Ten out of the 19 patients survived, and 9 died, with a 5-year survival rate of 62.8% and a 10-year survival rate of 56.5%. The main causes of death were hepatic disorders and sepsis.

SEGMENTAL DILATATION

Segmental dilatation of the intestine is a rare condition characterized by localized dilatation of the intestines without mechanical bowel obstruction and malformation of the intestinal nerve plexus. Since Swenson and Rathauser reported this condition as a 'new entity' in 1959,[34] various etiologies have been proposed. However, the clinical manifestations and pathological findings are diverse, and a unified disease concept has not been established. Therefore, it may be appropriate to consider it as a group of disorders presenting with localized intestinal dilatation.

Although approximately 50 cases have been reported in the literature in Japan, no large-scale survey has been conducted.[35] A nationwide survey conducted over 10 years from 2001 to 2010 identified 37 cases, including 26 definitive and 9 suspected cases. Based on a secondary survey of these cases, 28 were determined to be definitive, with 2 of the suspected cases added after discussions at meetings of the investigation group and general meetings. The commonly dilated segments were the ileum and colon (ileum 14 cases, colon 10 cases, jejunum 3 cases, duodenum 1 case). The most common onset period was neonatal, with 18 cases, including 7 diagnosed prenatally.

If this disease is not complicated by any other condition, resection of the lesion can significantly improve symptoms. Plain abdominal radiography successfully indicated the presence of lesions. A preoperative diagnosis also requires confirmation of segmental intestinal dilatation using contrast radiography or CT. When the dilatation site is located in the colon, it must be differentiated from HSCR. For the diagnosis of this disease, caliber change should be clearly observed at the oral side of the dilated segment by barium enema. If this is not clear, anorectal manometry or RMB is required for differentiation.

Resection of the dilated segment and end-to-end anastomosis of the intestine provide a good prognosis. Surgery was performed in 27 patients, with 1 patient awaiting surgery. In 26 of the 27 cases, resection of the dilated segment and intestinal anastomosis were performed. Of these 26 cases, enterostomy was performed in 4 cases and gastrostomy in 2 cases. These laparotomies were performed during the neonatal period in 13 cases (48%), during infancy in 4 cases (15%), during childhood in 5 cases (19%), and during school age in 3 cases (11%)

A total of 27 cases had a good prognosis. One patient with cerebral palsy died of sepsis due to a catheter infection.

INTERNAL ANAL SPHINCTER ACHALASIA

IASA causes persistent constipation due to inadequate relaxation of the internal anal sphincter despite the presence of ganglion cells in the rectal wall. The diagnostic criteria are as follows: (1) Patient has intractable constipation, (2) No rectal stricture on contrast enema, (3) Negative rectoanal reflex, (4) Presence of ganglion cells in an RMB specimen. This disease has been reported to account for 4.5% of chronic constipation in childhood and may be incorrectly diagnosed as chronic functional constipation.[36] In addition to medication, internal anal sphincter myotomy or myectomy and botulinum toxin injection are performed. The prognosis for this disease is favorable.

A total of six cases, including three cases from the primary nationwide survey conducted over 10 years from 2001 to 2010 and an additional three cases, were enrolled, and two met the above diagnostic criteria.

CHRONIC IDIOPATHIC INTESTINAL PSEUDO-OBSTRUCTION

CIIP is an intractable disease of unknown etiology, characterized by prolonged bowel obstructive symptoms, including abdominal distension, nausea, vomiting, and abdominal pain. A radiological examination reveals a dilated bowel and air fluid levels. Chronic intestinal pseudo-obstruction (CIPO) is defined as a functional

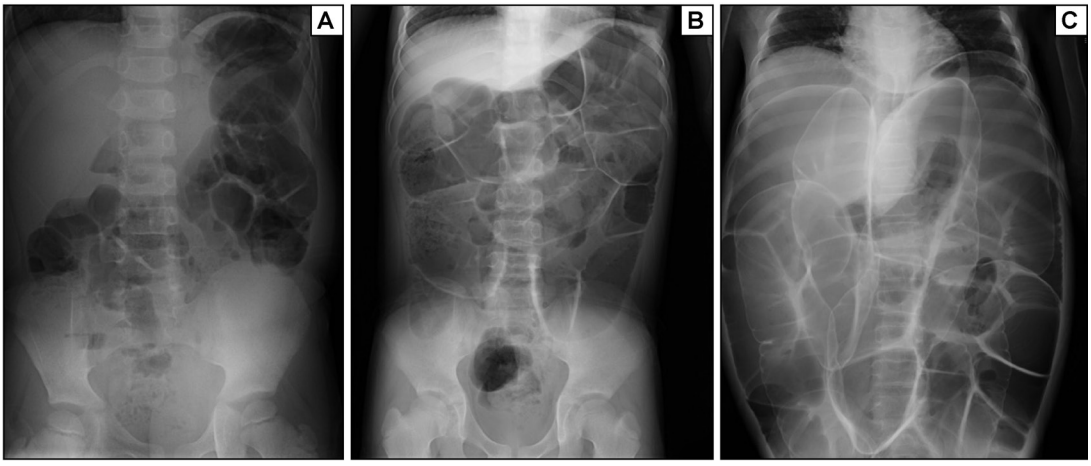

Figure 3 Abdominal X-rays of chronic idiopathic intestinal pseudo-obstruction. The patient remained asymptomatic until the age of 5 years. At 7 years of age, she experienced abdominal distention, which gradually worsened over time. By 11 years of age, her symptoms had become severe enough to necessitate ileostomy. Despite requiring home parenteral nutrition (HPN) due to the daily loss of 8000 mL of intestinal fluid through ileostomy, she has survived for >15 years postsurgery and continues to manage her daily life. (A) 5 years of age. (B) 7 years of age. (C) 11 years of age before ileostomy surgery. This X-ray image appears to show free air at first glance, but since there are no symptoms such as abdominal pain, it is considered to be observing a part of the intestinal gas.

motility disorder that presents with obstructive symptoms without mechanical obstruction, impeding the transport of gastrointestinal contents. CIPO is classified into three types: primary, caused by gastrointestinal lesions; secondary, associated with systemic illnesses or drugs; and idiopathic, with an unknown etiology.

In the diagnosis of adult CIIP, it is crucial to distinguish it from secondary CIPO.[37] In the adult medical field, this disease remains under-recognized, not only among general clinicians but also among gastroenterologists. Consequently, inappropriate clinical practice and unnecessary surgeries for bowel obstruction have been performed.[38] In contrast, in pediatric patients, many cases present with a neonatal onset, and the disease is recognized as a disorder related to HSCR. This section focuses on CIIP, which develops during childhood.

A nationwide survey conducted from 2001 to 2010 identified 92 primary enrollments in childhood-onset CIPO, with over 90% being idiopathic.[39] Of these, 56 met the diagnostic criteria for CIIP. This disease can develop sporadically, with peristaltic disorders potentially occurring at single or multiple sites along the gastrointestinal tract. Lesions manifesting as dilated intestines are frequently observed in the small bowel and the colon.

The primary initial symptoms in neonatal and infant-onset cases are abdominal distension and vomiting, while older children typically present with abdominal distension, vomiting, constipation, and diarrhea (figure 3). Adult patients often experience abdominal pain. In some instances of prolonged pseudo-obstructive symptoms, gastrointestinal rest may alleviate the condition. However, in most cases, the disease follows a pattern of remission and exacerbation, with overall progression of symptoms.

CIIP typically develops in the neonatal period or infancy and presents with symptoms of bowel obstruction that often require emergency operations for its diagnosis and treatment. In older children, this condition may progress gradually. Neonatal-onset and infant-onset cases necessitate differentiation from HSCR and other types of ADHD. Consequently, most patients undergo early intestinal full-thickness biopsy via laparotomy and gastrointestinal decompression with enterostomy shortly after onset. For cases with an onset in older childhood and adulthood, where intestinal full-thickness biopsy is not feasible, characteristic peristalsis disorders are assessed using cine MRI or manometry.[40] It is crucial to differentiate this condition from mechanical bowel obstruction or secondary intestinal pseudo-obstruction.

In many cases, the disease progresses with repeated cycles of remission and exacerbation. At first, treatment may begin with conservative approaches, such as drug therapy and intravenous/enteral nutrition, and then shift to invasive treatments, such as decompression via tubing or enterostomy, as the condition progresses. Surgical intervention is imperative in cases of intestinal perforation, necrosis, or severe enteritis. Even after enterostomy and resection of dilated segments, obstructive symptoms may recur in many cases owing to dysfunction of the remaining intestines. Therefore, in some cases, multiple surgeries, including exploratory laparotomy, enterostomy, intestinal resection, and enterostomy closure, may be performed. In a few cases, small bowel transplantation may be considered when conservative treatments become ineffective due to complications or prolonged pain.

Although the prognosis is relatively good, repeated long-term hospitalization is often necessary. Even for outpatients, intravenous/enteral nutrition support and

enterostomy management can significantly limit the patient's daily life. When gastrointestinal decompression is ineffective, intestinal perforation or enteritis can lead to sepsis, potentially resulting in death.

According to a nationwide survey in Japan, of the 56 cases that met the diagnostic criteria, 53 (94.2%) showed long-term survival, although only a small proportion showed an improvement in their condition.[41] The average duration of symptoms was 14.6 years, with an increasing number of patients transitioning to adult CIIP. Nearly half of these cases require gastrointestinal decompression via gastrostomy, enterostomy, or tubing. Moreover, 74% of patients require some form of nutritional support, including parenteral and/or enteral nutrition.

FUTURE PERSPECTIVES AND CONCLUSIONS

Notably, HSCR involving the small intestine, IHG, CIPO, and MMIHS has a poor prognosis. Ultimately, small-bowel transplantation is necessary for refractory cases, but it is highly invasive, and outcomes are less than optimal despite advances in surgical techniques and management. According to the data from the international transplant registry, a total of 2010 children received 2080 intestinal transplants from 1985 to 2017. Overall, the 1-year and 5-year patient/graft survival rates were 72.7%/66.1% and 57.2%/47.8%, respectively.[42]

Thus, regenerative therapy has emerged as a potential form of treatment involving regeneration of the enteric nervous system, mesenchyme, and smooth muscle in the affected areas.[43] Further research is needed to improve patient outcomes in this area.

ADHD requires long-term parenteral nutrition. The development of parenteral nutrition has contributed to prolonged life expectancy in patients with intestinal failure, including ADHD.[8 44 45] Since the clinical application of regenerative medicine takes time, it is necessary to search for safer methods of parenteral nutrition in basic and clinical experiments.[46–49]

Acknowledgements The authors thank Mr. Brian Quinn for his comments on this manuscript

Contributors SO and SI contribute to the conception or design of the work, the acquisition, analysis, or interpretation of data for the work, draft and revise the work. SI contribute to the final approval of the version to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The ethical guidelines of clinical research of the Japanese Ministry of Health, Labor, and Welfare used the figures in this review. It was approved by the Research Ethics Committee of Kagoshima University Hospital (registration number: 230172).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing is not applicable as no data sets were generated and/or analysed for this study.

ORCID iDs
Shun Onishi http://orcid.org/0000-0002-3984-3764
Satoshi Ieiri http://orcid.org/0000-0002-1250-093X

REFERENCES

1 Muto M, Matsufuji H, Taguchi T, *et al*. Japanese clinical practice guidelines for allied disorders of Hirschsprung's disease, 2017. *Pediatr Int* 2018;60:400–10.
2 Taguchi T, Ieiri S, Miyoshi K, *et al*. The incidence and outcome of allied disorders of Hirschsprung's disease in Japan: Results from a nationwide survey. *Asian J Surg* 2017;40:29–34.
3 RavitchMM. Hirshsprung's disease; the clinical differentiation and treatment of children with Hirschsprung's disease and pseudo-Hirschsprung's disease. *Calif Med* 1958;89:7–13.
4 Puri P. Variant Hirschsprung's disease. *J Pediatr Surg* 1997;32:149–57.
5 Holschneider AM, Puri P. *Hirschsprung's Disease and Allied Disorders*. 2nd edn. xvi. Harwood Academic Marston, 1999:503.
6 Taguchi T, Matsufuji M, Ieiri S. *Hirschsprung's Disease and the Allied Disorders: Status Quo and Future Prospects of Treatment*. 1st edn. NYC, NY: Springer, 2019.
7 The Ministry of Health LaWoJ, Health Labour Sciences Research Grant in fiscal years 2014-2016: Tomoaki Taguchi's group. Clinical practice guidelines for allied disorders of hirschsprung's disease –practical version. 2017. Available: https://www.jspghan.org/guide/hirschsprungs.html [Accessed 28 Aug 2024].
8 Yano K, Muto M, Sugita K, *et al*. Prognostic factors for pediatric patients with severe intestinal motility disorders: a single institution's experience. *Surg Today* 2025;55:380–5.
9 Yoshimaru K, Yanagi Y, Obata S, *et al*. Acetylcholinesterase staining for the pathological diagnosis of Hirschsprung's disease. *Surg Today* 2021;51:181–6.
10 Knowles CH, Farrugia G. Gastrointestinal neuromuscular pathology in chronic constipation. *Best Pract Res Clin Gastroenterol* 2011;25:43–57.
11 Zani A, Eaton S, Morini F, *et al*. European Paediatric Surgeons' Association Survey on the Management of Hirschsprung Disease. *Eur J Pediatr Surg* 2017;27:96–101.
12 Tran VQ, Lam KT, Truong DQ, *et al*. Diagnostic value of rectal suction biopsies using calretinin immunohistochemical staining in Hirschsprung's disease. *J Pediatr Surg* 2016;51:2005–9.
13 Jiang M, Li K, Li S, *et al*. Calretinin, S100 and protein gene product 9.5 immunostaining of rectal suction biopsies in the diagnosis of Hirschsprung' disease. *Am J Transl Res* 2016;8:3159–68.
14 Romero P, Burger A, Wennberg E, *et al*. Clinical Relevance of Pathological Diagnosis of Hirschsprung's Disease with Acetylcholine-Esterase Histochemistry or Calretinin Immunohistochemistry. *Children (Basel)* 2024;11:428.
15 Jeong H, Jung HR, Hwang I, *et al*. Diagnostic Accuracy of Combined Acetylcholinesterase Histochemistry and Calretinin Immunohistochemistry of Rectal Biopsy Specimens in Hirschsprung's Disease. *Int J Surg Pathol* 2018;26:507–13.
16 Yoshimaru K, Taguchi T, Obata S, *et al*. Immunostaining for Hu C/D and CD56 is useful for a definitive histopathological diagnosis of congenital and acquired isolated hypoganglionosis. *Virchows Arch* 2017;470:679–85.
17 Toyosaka A, Okamoto E, Okasora T, *et al*. Clinical, laboratory and prognostic features of congenital large intestinal motor dysfunction (pseudo-Hirschsprung's disease). *Clin Auton Res* 1993;3:243–8.
18 Ieiri S, Miyoshi K, Nagata K, *et al*. Current clinical features in diagnosis and treatment for immaturity of ganglia in Japan: analysis from 10-year nationwide survey. *Pediatr Surg Int* 2015;31:949–54.
19 Taguchi T, Masumoto K, Ieiri S, *et al*. New classification of hypoganglionosis: congenital and acquired hypoganglionosis. *J Pediatr Surg* 2006;41:2046–51.
20 Yoshimaru K, Tamaki A, Matsuura T, *et al*. Palisading-like arrangement of immature ganglion cell in myenteric ganglia is a unique pathological feature of immaturity of ganglia. *J Pediatr Surg* 2022;57:1269–73.
21 Yamataka A, Fujiwara T, Nishiye H, *et al*. Localization of intestinal pacemaker cells and synapses in the muscle layers of a patient with colonic hypoganglionosis. *J Pediatr Surg* 1996;31:584–7.
22 Tamaki A, Kohashi K, Yoshimaru K, *et al*. A Novel Objective Pathologic Criterion for Isolated Hypoganglionosis. *Am J Surg Pathol* 2024;48:803–12.

23 Watanabe Y, Sumida W, Takasu H, *et al*. Early jejunostomy creation in cases of isolated hypoganglionosis: verification of our own experience based on a national survey. *Surg Today* 2015;45:1509–12.
24 Yamada Y, Mori T, Takahashi N, *et al*. Historical Cohort Study of Congenital Isolated Hypoganglionosis of the Intestine: Determining the Best Surgical Interventions. *Biomolecules* 2023;13:1560.
25 Watanabe Y, Kanamori Y, Uchida K, *et al*. Isolated hypoganglionosis: results of a nationwide survey in Japan. *Pediatr Surg Int* 2013;29:1127–30.
26 Fadda B, Maier WA, Meier-Ruge W, *et al*. Neuronal intestinal dysplasia. Critical 10-years' analysis of clinical and biopsy diagnosis. *Z Kinderchir* 1983;38:305–11.
27 Taguchi T, Kobayashi H, Kanamori Y, *et al*. Isolated intestinal neuronal dysplasia Type B (IND-B) in Japan: results from a nationwide survey. *Pediatr Surg Int* 2014;30:815–22.
28 Terra SA, Gonçalves AC, Lourenção PLTA, *et al*. Challenges in the diagnosis of intestinal neuronal dysplasia type B: A look beyond the number of ganglion cells. *World J Gastroenterol* 2021;27:7649–60.
29 Meier-Ruge W. Casuistic of colon disorder with symptoms of Hirschsprung's disease (author's transl). *Verh Dtsch Ges Pathol* 1971;55:506–10.
30 Kobayashi H, Hirakawa H, Puri P. Is intestinal neuronal dysplasia a disorder of the neuromuscular junction? *J Pediatr Surg* 1996;31:575–9.
31 Kobayashi H, Hirakawa H, Surana R, *et al*. Intestinal neuronal dysplasia is a possible cause of persistent bowel symptoms after pull-through operation for Hirschsprung's disease. *J Pediatr Surg* 1995;30:253–7.
32 Puri P, Gosemann JH. Variants of Hirschsprung disease. *Semin Pediatr Surg* 2012;21:310–8.
33 Soh H, Fukuzawa M, Kubota A, *et al*. Megacystis microcolon intestinal hypoperistalsis syndrome: A report of a nationwide survey in Japan. *J Pediatr Surg* 2015;50:2048–50.
34 Swenson O, Rathauser F. Segmental dilatation of the colon; a new entity. *Am J Surg* 1959;97:734–8.
35 Sakaguchi T, Hamada Y, Masumoto K, *et al*. Segmental dilatation of the intestine: results of a nationwide survey in Japan. *Pediatr Surg Int* 2015;31:1073–6.
36 Obata S, Fukahori S, Yagi M, *et al*. Internal anal sphincter achalasia: data from a nationwide survey of allied disorders of Hirschsprung's disease in Japan. *Surg Today* 2017;47:1429–33.
37 Iida H, Ohkubo H, Inamori M, *et al*. Epidemiology and clinical experience of chronic intestinal pseudo-obstruction in Japan: a nationwide epidemiologic survey. *J Epidemiol* 2013;23:288–94.
38 Tanaka K, Ohkubo H, Yamamoto A, *et al*. Natural History of Chronic Intestinal Pseudo-obstruction and Need for Palliative Care. *J Neurogastroenterol Motil* 2023;29:378–87.
39 Muto M, Matsufuji H, Tomomasa T, *et al*. Pediatric chronic intestinal pseudo-obstruction is a rare, serious, and intractable disease: a report of a nationwide survey in Japan. *J Pediatr Surg* 2014;49:1799–803.
40 Fuyuki A, Ohkubo H, Higurashi T, *et al*. Clinical importance of cine-MRI assessment of small bowel motility in patients with chronic intestinal pseudo-obstruction: a retrospective study of 33 patients. *J Gastroenterol* 2017;52:577–84.
41 Hashizume N, Yagi M, Ushijima K, *et al*. Pharmacotherapy for pediatric chronic intestinal pseudo-obstruction: Nationwide survey in Japan. *Pediatr Int* 2017;59:467–72.
42 Raghu VK, Beaumont JL, Everly MJ, *et al*. Pediatric intestinal transplantation: Analysis of the intestinal transplant registry. *Pediatr Transplant* 2019;23:e13580.
43 Yoshimaru K, Matsuura T, Uchida Y, *et al*. Cutting-edge regenerative therapy for Hirschsprung disease and its allied disorders. *Surg Today* 2024;54:977–94.
44 Kaji T, Kawano T, Yamada W, *et al*. The changing profile of safe techniques for the insertion of a central venous catheter in pediatric patients - improvement in the outcome with the experiences of 500 insertions in a single institution. *J Pediatr Surg* 2016;51:2044–7.
45 Kaji T, Nakame K, Machigashira S, *et al*. Predictors of a successful outcome for infants with short bowel syndrome: a 30-year single-institution experience. *Surg Today* 2017;47:1391–6.
46 Onishi S, Kaji T, Yamada W, *et al*. The administration of ghrelin improved hepatocellular injury following parenteral feeding in a rat model of short bowel syndrome. *Pediatr Surg Int* 2016;32:1165–71.
47 Tsuruno Y, Nagano A, Sugita K, *et al*. Favorable inhibitory effect of clodronate on hepatic steatosis in short bowel syndrome model rats. *Pediatr Surg Int* 2024;40:307.
48 Machigashira S, Kaji T, Onishi S, *et al*. The protective effect of fish oil lipid emulsions on intestinal failure-associated liver disease in a rat model of short-bowel syndrome. *Pediatr Surg Int* 2018;34:203–9.
49 Machigashira S, Kaji T, Onishi S, *et al*. What is the optimal lipid emulsion for preventing intestinal failure-associated liver disease following parenteral feeding in a rat model of short-bowel syndrome? *Pediatr Surg Int* 2021;37:247–56.