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Guidelines

Japanese clinical practice guidelines for allied disorders of Hirschsprung's disease, 2017

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Abstract ***Background*:** Despite the presence of ganglion cells in the rectum, some patients have symptoms similar to those of Hirschsprung's disease. A consensus has yet to be established regarding the terminology for these diseases. We defined this group of diseases as "allied disorders of Hirschsprung's disease" and compiled these guidelines to facilitate accurate clinician diagnosis and provide appropriate treatment strategies for each disease.

***Methods*:** These guidelines were developed using the methodologies in the Medical Information Network Distribution System (MINDS). Of seven allied disorders, isolated hypoganglionosis; megacystis-microcolon-intestinal hypoperistalsis syndrome; and chronic idiopathic intestinal pseudo-obstruction were selected as targets of clinical questions (CQ). In a comprehensive search of the Japanese- and English-language articles in PubMed and Ichu-Shi Web, 836 pieces of evidence related to the CQ were extracted from 288 articles; these pieces of evidence were summarized in an evidence table.

***Results*:** We herein outline the newly established Japanese clinical practice guidelines for allied disorders of Hirschsprung's disease. Given that the target diseases are rare and intractable, most evidence was drawn from case reports and case series. In the CQ, the diagnosis, medication, nutritional support, surgical therapy, and prognosis for each disease are given. We emphasize the importance of full-thickness intestinal biopsy specimens for the histopathological evaluation of enteric ganglia. Considering the practicality of the guidelines, the recommendations for each CQ were created with protracted discussions among specialists.

***Conclusions*:** Clinical practice recommendations for allied disorders of Hirschprung's disease are given for each CQ, along with an assessment of the current evidence. We hope that the information will be helpful in daily practice and future studies.

Key words allied disorder of Hirschsprung's disease, chronic idiopathic intestinal pseudo-obstruction, clinical practice guideline, isolated hypoganglionosis, megacystis microcolon intestinal hypoperistalsis syndrome.

Hirschsprung's disease is a well-recognized disease characterized by the disordered transit of intestinal content, delayed meconium excretion, abdominal distention, bilious vomiting, constipation, and intestinal dilatation (megacolon) of the proximal bowel, resulting from dysperistalsis and a lack of rectoanal reflex due to aganglionosis at the most distal segment of intestine.

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Despite the presence of ganglion cells in the rectum, some patients have symptoms similar to those of Hirschsprung's disease. Ravitch first described such cases as "pseudo Hirschsprung's disease" in the *Annals of Surgery* in 1958.[1] Since then, various terminologies have been used to describe this group of diseases, including Hirschsprung's disease-related disorders, variant Hirschsprung's disease, allied disorders of Hirschsprung's disease, and Hirschsprung's disease-related neuromuscular disorders of the intestine.[2–5] In 1988, the first survey in Japan, which was published in the *Journal of the Japanese Society of Pediatric Surgeons*, referred to "pseudo-Hirschsprung's disease and related disorders".[6] In Japan, it has also been referred to as "allied disorders of Hirschsprung's disease",[7] and a consensus has not been established.

Purpose of the guidelines

The disease concepts and individual diseases included in the allied disorders of Hirschsprung's disease have gradually changed over time. Some of the diseases are recognized as rare, serious and intractable; thus, there is a need for supportive information, such as diagnostic criteria and treatment strategies that can be applied in the clinical setting. There are currently, however, no clinical practice guidelines for allied disorders of Hirschsprung's disease. The Allied Disorders of Hirschsprung's Disease Guideline Establishment Group, Research Project on Measures for Intractable Diseases, Health Labour Sciences Research Grant in 2014–2016 Fiscal Year, has compiled a set of guidelines in order to facilitate prompt clinician diagnosis and to provide appropriate treatment strategies for each disease. The essence of the newly proposed Japanese clinical guidelines for allied disorders of Hirschsprung's disease is summarized in this report.

Definition of allied disorders of Hirschsprung's disease

The term "allied disorders of Hirschsprung's disease" refers to a disease group that is characterized by symptoms and signs similar to those of Hirschsprung's disease, such as bowel obstruction, intestinal dilatation, and chronic constipation, despite the presence of ganglionic cells in the rectum.

Specialists in this disease group, including pediatric surgeons, pediatricians, pathologists, and physicians from the adult domain, have repeatedly discussed the disease concept and the classification. The following seven diseases are defined as allied disorders of Hirschsprung's disease: (i) immaturity of ganglia; (ii) isolated hypoganglionosis; (iii) intestinal neuronal dysplasia (IND); (iv) megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS); (v) segmental dilatation of intestine; (vi) internal anal sphincter achalasia (IASA); and (vii) chronic idiopathic intestinal pseudo-obstruction (CIIP; Table 1).

Guideline formulation

The guidelines were developed using the methodologies described in the *Medical Information Network Distribution System (Minds) Handbook for Clinical Practice Guideline Development 2014*[8] and the *Minds Manual for Clinical Practice Guideline Development.*[9]

Table 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 (HE or AchE staining)
(4) Megacystis microcolon intestinal hypoperistalsis syndrome
(5) Segmental dilatation of intestine
(6) Internal anal sphincter achalasia
(7) Chronic idiopathic intestinal pseudo-obstruction

AchE, acetylcholinesterase; HE, hematoxylin and eosin.

While patients with allied disorders of Hirschsprung's disease present with symptoms of bowel obstruction, the diseases are not associated with aganglionosis. For this reason, a histological evaluation of the enteric ganglions plays the most important role in determining the appropriate clinical practice for allied disorders of Hirschsprung's disease. Thus, a pathology approach is emphasized in the guidelines.

Four allied disorders of Hirschsprung's disease (immaturity of ganglia [intramural ganglion cells are sufficient in number but are small and markedly immature]; IND [presence of submucosal giant ganglia, ≥9 neurocytes in one ganglion; and proliferation of acetylcholinesterase (AchE)-positive nerve fibers]; segmental dilatation of intestine [normal distribution of the nerve plexus is present]; and IASA [normal ganglion cells present on rectal mucosal biopsy]) are considered to be extremely rare, but they have a favorable clinical course and are unlikely to cause confusion in the clinical setting with regard to treatment decisions. The other three diseases (isolated hypoganglionosis, MMIHS, and CIIP) are also rare diseases for which there is no established treatment. Quite a few cases have been documented and their clinical course is considered to be serious. Thus, when these three diseases are encountered in the clinical setting, evidence should be considered and specialist opinions should be obtained. For these reasons, isolated hypoganglionosis, MMIHS, and CIIP were selected as the targets of the clinical questions (CQ) of the guidelines.

Systematic review

We expected it to be difficult to obtain high-quality evidence on each intractable disease in the CQ, because of the small number of cases available for evaluation; thus, a unique approach was used for the systematic review (SR).[10]

There are only a few reports on the rare diseases in the CQ. Sometimes the three diseases were duplicated or confused in a single paper. In addition, a scoping search showed that the majority of the articles were case reports. Many of the case reports included descriptions on the diagnosis, treatment, prognosis, and complications. In order to utilize these articles without disregarding them as low-evidence-level studies, we decided to conduct an individual search for each CQ; the search should target the three diseases collectively; and that the outcomes would then be assigned to each CQ.

The PubMed and Ichu-Shi Web databases were used. The scope included Japanese- and English-language articles published until 2015. A total of 1,488 articles were obtained, and 836 pieces of evidence were extracted from 288 selected articles through screening by 10 SR team members. The extracted evidence was classified into the CQ of each of the target diseases. This method focused on the total pieces of evidence and provided a different measurement of the evidence to that obtained in conventional studies.

Creation of recommendations

The guideline development group created the recommendations and commentary based on the materials submitted by the SR team.

Given that most of the evidence was obtained from case reports and case series, the strength of the evidence was mostly "D" (very weak); the aim, however, was to provide recommendations that would be useful for clinical practice. When creating the recommendations, the opinions from the guideline development committee members, as specialists, were considered to be extremely important. In the process of forming a consensus, 13 committee members held protracted discussions. Then, in order to prevent the opinions from relying too heavily on their individual experience, the recommendations were decided on using the Delphi voting method.[10]

SCOPE on allied disorders of Hirschsprung's disease

Diagnosis

CQ1-1: How is isolated hypoganglionosis diagnosed?

Recommendation. A full-thickness biopsy of the gastrointestinal tract (especially the small intestine and sigmoid colon) is recommended for the definitive diagnosis of isolated hypoganglionosis (1C = strong recommendation, based on weak evidence).

Isolated hypoganglionosis is the most difficult disease to diagnose among the allied disorders of Hirschsprung's disease. This is because the basic disease concept is not clear, and a definitive method of making a diagnosis has not been clearly established. Although the whole-mount preparation of the neural plexus would be preferable for the morphological observation of the myenteric plexus (Auerbach's plexus), diagnosis of isolated hypoganglionosis has been based on the detection of a reduced number of neurocytes in the plexus. Many studies have shown the usefulness of a full-thickness gastrointestinal biopsy (especially from the small and large bowels) in the diagnosis of isolated hypoganglionosis.[11–28] When it is difficult to assess the neurocyte distribution on hematoxylin and eosin (HE) staining, histochemical staining (i.e. AchE, Hu C/D antibody, nicotinamide adenine dinucleotide phosphate [NADPH], succinate dehydrogenase [SDH], lactate dehydrogenase [LDH], silver staining etc.) is useful for the diagnosis.[22–28] The presence of ≤20 Hu C/D-positive cells in the muscularis propria per centimeter of resected intestinal specimen is significantly lower than that noted in the normal intestinal tract. Hu C/D may be useful for identifying a decrease in the number of ganglion cells. No complications have been reported in association with full-thickness biopsies. The recommended strategy for the pathology investigation is given in Table 2.

Table 2 Strategy for the pathological diagnosis of isolated hypoganglionosis

(1) In the neonatal period, it is sufficient to rule out aganglionosis using full-thickness intestinal specimens collected from the jejunum or ileum (both if possible) and sigmoid colon
(2) At the second laparotomy after 2 months of age (i.e. when changing a double-barrel fistula into a Bishop–Koop type fistula), the decrease in the number of ganglionic cells should be confirmed with a specimen of the entire intestinal circumference (whole-mount preparation)

The size of intestinal nerve plexus is small and the number of ganglion cells is low in patients with isolated hypoganglionosis. The individual ganglion cells are small during the neonatal period, but they grow over time as the patient matures, although their number will never increase. The number of Hu C/D-positive cells is significantly decreased in isolated hypoganglionosis, and it may be considered as a key staining finding on pathology, to allow for an accurate and prompt diagnosis of the disease.

CQ1-2: How is MMIHS diagnosed?

Recommendation. For cases in which symptoms of bowel obstruction, such as abdominal distension and vomiting, are present during the neonatal period and no organic obstruction is observed, a gastrointestinal series is recommended. When microcolon is observed and megalocystis is simultaneously confirmed on cystography, computed tomography (CT), or ultrasonography, MMIHS is strongly suspected. An intestinal full-thickness biopsy is recommended for the definitive diagnosis to differentiate it from other allied disorders of Hirschsprung's disease (1C = strong recommendation, based on weak evidence).

In recent years, prenatal diagnoses have often been made based on a dilated intestinal tract and megalocystis.[29,30] Cystography can be useful for a clear diagnosis of megalocystis, but no further clinical information can be obtained by this modality. Ultrasonography or CT can also be used to diagnose megalocystis. Enema is useful for the confirmation of microcolon, which is an indispensable sign of this disease. In many cases, laparotomy is performed during the neonatal period due to severe abdominal distension. Full-thickness intestinal biopsy is indispensable during laparotomy, because it must be differentiated from other allied disorders of Hirschsprung's disease, such as isolated hypoganglionosis and CIIP. MMIHS is characterized by the absence of ganglion cell abnormalities.[31–33] The diagnostic criteria are listed in Table 3.

CQ1-3: How is CIIP diagnosed?

Recommendation. The duration of symptoms and the bowel obstruction 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 on diagnostic imaging. For children, an intestinal full-thickness

Table 3 Diagnostic criteria for megacystis microcolon intestinal hypoperistalsis syndrome

(1) Symptoms of bowel obstruction, such as abdominal distension, vomiting, and abdominal pain, which are present immediately after birth
(2) Megacystis present
(3) Barium enema indicates microcolon in the neonatal period
(4) No mechanical obstructive lesions observed in the gastrointestinal tract
(5) No pathological abnormalities observed in the neural plexus of a full-thickness intestinal biopsy specimen

Table 4 Diagnostic criteria for chronic idiopathic intestinal pseudo-obstruction

The following 7 items need to be satisfied:
(1) Persistent or repetitive development, over a long period of time, of symptoms of serious bowel obstruction that may require hospitalization, such as abdominal distension, nausea and vomiting, abdominal pain etc
(2) Duration of symptoms ≥2 months for neonatal onset and ≥6 months for onset in infancy or later (including adults)
(3) Gastrointestinal dilatation and air–fluid level noted on diagnostic imaging[†]
(4) No lesions mechanically blocking the gastrointestinal tract
(5) No pathological abnormalities in the nerve plexuses on HE-stained full-thickness intestinal biopsy specimens[‡]
(6) Megacystis microcolon intestinal hypoperistalsis syndrome and segmental dilatation of intestine are excluded
(7) Secondary chronic intestinal pseudo-obstruction is excluded[§]

[†]For neonates, confirmation of the air–fluid level on plain abdominal radiography in a standing or lateral decubitus position may be difficult, therefore this is not necessarily required. [‡]For adults, when an intestinal full-thickness biopsy is unobtainable, a characteristic peristalsis disorder should be confirmed by manometry or cine magnetic resonance imaging. [§]Systemic illness or drug-induced functional ileus (Table 5) need to be ruled out, especially for adult cases. HE, hematoxylin and eosin.

biopsy is recommended for definitive diagnosis in order to differentiate it from other allied disorders of Hirschsprung's disease. For adults, it is important to differentiate mechanical obstruction and secondary intestinal pseudo-obstruction from idiopathic pseudo-obstruction, and a full-thickness biopsy is not usually conducted. (1D = strong recommendation, based on very weak evidence).

Intestinal dilatation and air–fluid levels, and non-mechanical obstruction are diagnosed on plain abdominal X-ray, CT, magnetic resonance imaging (MRI), or similar modalities.[34–36] Pathology evaluation on full-thickness bowel biopsy is indispensable for the differential diagnosis of isolated hypoganglionosis and immaturity of ganglia.[35,36] Idiopathy is confirmed when conventional histology, such as HE staining, fails to show a meaningful pathology.[36–41] Cine MRI and intestinal manometry are useful for assessing peristaltic disorders present in CIIP, and these two examinations are used instead of full-thickness biopsy in adults.[40–44] The diagnostic criteria are listed in Table 4.

Table 5 Secondary chronic intestinal pseudo-obstruction

Gastrointestinal smooth muscle-related diseases
Systemic sclerosis
Dermatomyositis
Multiple myositis
Systemic lupus erythematosus
Mixed connective tissue disease
Ehlers–Danlos syndrome
Muscular dystrophy
Amyloidosis
Small bowel-based lymphoid infiltration
Brown bowel syndrome (ceroidosis)
Mitochondrial encephalomyopathy
Gastrointestinal nerves-related diseases
Familial dysautonomia
Primary dysautonomia
Diabetic neuropathy
Myotonic dystrophy
Pseudo-obstruction after infection, such as EBV, Herpes zoster virus, and rotavirus
Endocrine diseases
Hypothyroidism
Hypoparathyroidism
Pheochromocytoma
Metabolic diseases
Uremia
Porphyria
Serious electrolytes abnormality (K^+, Ca^{2+}, Mg^{2+})
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
Drug-induced diseases
Antidepressant
Anti-anxiety drug
Anthraquinone-based laxative
Phenothiazine drugs
Vinca alkaloid
Anticholinergic drug
Opioid
Ca channel blocker
Verapamil

Functional ileus caused by systemic illness or the aforementioned drugs needs to be ruled out for the diagnosis of idiopathy. EBV, Epstein–Barr virus; HE, hematoxylin and eosin.

Drug therapy

CQ2-1: What kind of drug therapy is recommended for the treatment of isolated hypoganglionosis?

Recommendation. No drug therapy is recommended for isolated hypoganglionosis at this point (D = no definite recommendation, based on very weak evidence).

At present, based on the available evidence, no drug can be recommended as an effective agent that improves gastrointestinal functional disorder or the symptoms accompanying isolated hypoganglionosis.

Drug treatment for isolated hypoganglionosis is carried out in various institutions and includes prokinetic agents, probiotics, Japanese herbal medicine (daikenchuto), antibiotics, enemas, laxatives, and antidiarrheal drugs. No randomized controlled trials (RCT) or case series, however, have described the efficacy of these treatments. Note that no adverse events have been reported in association with any of the abovementioned drugs.

CQ2-2: What kind of drug therapy is recommended for MMIHS?

Recommendation. Although the usefulness of Japanese herbal medicine (daikenchuto) and probiotics in the treatment MMIHS has been reported, the evidence to recommend this treatment is currently insufficient (D = no definite recommendation, based on very weak evidence).

Prokinetic agents (e.g. cisapride, metoclopramide), probiotics, Japanese herbal medicine (daikenchuto), antibiotics (e.g. erythromycin), enemas, laxatives, and antidiarrheal drugs are sometimes used to treat MMIHS, but there are no RCT or case series to support their efficacy. Daikenchuto has been reported to induce improvement in gastrointestinal motility and intestinal transit time,[45] to increase the enteral nutrition intake,[46] and to improve the symptoms of bowel obstruction.[47,48] The administration of probiotics via lower jejunostomy has been reported to prevent enteritis.[49] Note that no adverse events have been reported in association with any of the aforementioned drugs.

CQ2-3: What kind of drug therapy is recommended for the treatment of CIIP?

Recommendation. Prucalopride, cisapride, Japanese herbal medicines (daikenchuto), probiotics, and antibiotics (erythromycin) are sometimes used for the treatment of CIIP, and some reports have shown the usefulness of those agents for the treatment of functional gastrointestinal disorder or abdominal symptoms. The evidence to recommend this treatment, however, is currently insufficient (D = no definite recommendation, based on very weak evidence).

There have been few RCT or case series to support the efficacy of these agents in the control of CIIP; most of the available articles are case reports. Probiotics have been reported to increase the intake of enteral nutrition and to reduce the incidence of enteritis in two case reports.[50,51] Erythromycin used with the expectation of enhancing intestinal motility has been reported to increase the enteral nutrition intake and to improve the symptoms of bowel obstruction in four case reports.[47,48,52,53] No reports have described probiotics or erythromycin as ineffective, and neither probiotics nor erythromycin have been associated with any adverse events. Although there are no recommended medications, treatment with probiotics and erythromycin may be attempted in cases of CIIP.

Intestinal decompression

Intestinal decompression is defined as the drainage of the gastrointestinal contents via enterostomy, gastrostomy, a nasogastric tube, a long tube, or a trans-anal tube in order to relieve intragastrointestinal pressure.

CQ3-1: Is gastrointestinal decompression recommended for the treatment of isolated hypoganglionosis?

Recommendation. Upper jejunostomy is suggested for isolated hypoganglionosis. Ileostomy may be effective in some cases, but the efficacy of enterostomy at any other part of the intestinal tract is unknown (2C = weak recommendation, based on weak evidence).

Effective gastrointestinal decompression may enable enteral feeding and fulfil the expectation of growth and long-term survival. Concomitant decompression via gastrostomy and high jejunostomy enabled enteral nutrition in one case: intestinal lavage was empirically performed at the time of exacerbation in this case.[54] The prognosis varies depending on the location of the enterostomy. Compared with ordinary jejunostomy and ileostomy, high jejunostomy is significantly more effective with regard to X-ray findings, survival rate,[55] and the incidence of bowel obstruction.[56] Isolated hypoganglionosis patients who underwent high jejunostomy had good outcomes.[54,57] The effectiveness of ileostomy is unclear. In some cases it improved bowel obstruction,[57] in other cases ileectomy was required due to functional failure,[58] and in other cases re-construction of the enterostomy was required at a higher position.[56] There are no reports on effective colostomy, and additional enterostomies were required in the reported cases.[56,59]

CQ3-2: Is gastrointestinal decompression therapy recommended for the treatment of MMIHS?

Recommendation. There is no evidence to support the positive recommendation of gastrointestinal decompression for MMIHS (D = no definite recommendation, based on very weak evidence).

Regarding gastrointestinal decompression therapy for MMIHS, some reports have shown that tube decompression did not improve the symptoms,[60] and enteral feeding was not enabled by decompression via gastrostomy, even with simultaneous enterostomy,[61] despite its efficacy for isolated hypoganglionosis. Regarding intestinal lavage, there was a case in which switching from transanal lavage to antegrade lavage by Malone surgery enabled a patient to receive home care.[49] Regardless of the enterostomy site, enterostomy can only temporarily[62] or

partially[48] relieve symptoms and does not improve the prognosis.[63] Colostomy is reported to be ineffective.[62]

CQ3-3: Is gastrointestinal decompression effective for CIIP?

Recommendation. Intermittent decompression via an enteric tube may be effective in some cases of CIIP, and enterostomy may be effective in others. The appropriate approach should be considered on a case-by-case basis (2D = weak recommendation, based on very weak evidence).

In one case remission from the symptoms of bowel obstruction was reportedly achieved and nasogastric tube and enteral nutrition was enabled, but the symptoms of bowel obstruction recurred.[64] With regard to the use of an ileus tube, one patient had marked improvement of abdominal distension and abdominal pain,[65] but there have been some cases in which ileus tubes proved ineffective[66] and in which intestinal dilatation showed no improvement.[67] There have been cases in which the oral intake was enabled by intestinal lavage and continuous decompression through enterostomy,[68] in which high jejunostomy temporarily improved the symptoms of bowel obstruction and enabled a small amount of oral intake,[69] and in which ileostomy was reported to be effective.[67,69] Nevertheless, the ineffectiveness of enterostomy has also been reported.[48] Colostomy has not been shown to be effective in any cases and it did not improve the symptoms of bowel obstruction, even with simultaneous ileostomy.[69]

Nutrition therapy

CQ4-1: Are enteral nutrition and parenteral nutrition effective as nutrition treatment for isolated hypoganglionosis?

Recommendation. Enteral nutrition and parenteral nutrition are recommended as nutrition treatment for isolated hypoganglionosis (1D = strong recommendation, based on very weak evidence).

Very few articles have discussed nutrition treatment for isolated hypoganglionosis. The evidence level is very low. This disease can develop during the neonatal period. In the clinical setting, parenteral nutrition therapy is administered from an early stage in most cases. This is combined with enteral feeding once the disease condition has stabilized after stoma construction. The recommendation of parenteral nutrition and enteral nutrition as nutrition treatments is considered to be appropriate. Nutrition therapy should be considered in combination with surgical treatment and medication for this disease.

CQ4-2: Are enteral nutrition and parenteral nutrition useful for MMIHS?

Recommendation. Enteral nutrition and parenteral nutrition are recommended for MMIHS (1D = strong recommendation, based on very weak evidence).

Peristaltic dysfunction develops during the neonatal period. It is difficult to save the lives of children with MMIHS without any parenteral or enteral nutrition support. Although the evidence level is low, parenteral and enteral nutrition are considered appropriate for this disease. Physicians need to be aware of the potential for complications of long-term parenteral nutrition, such as catheter-related bloodstream infection, cholestatic liver dysfunction, and portal hypertension, and appropriate preventative measures and treatments should be implemented.[62] Regarding enteral nutrition for this disease, further investigations are needed to determine which method is most effective and which nutrients are appropriate.

CQ4-3: Are enteral nutrition and parenteral nutrition effective for CIIP?

Recommendation. Enteral nutrition and parenteral nutrition are recommended for CIIP (1D = strong recommendation, based on very weak evidence).

Intestinal peristaltic disorder may persist for a long period of time, and some kind of nutrition therapy is indispensable for CIIP. Thus, the recommendation of nutrition therapy for this disease is deemed appropriate. Physicians should pay special attention to the development of complications related to long-term parenteral nutrition. Regarding enteral nutrition, some semi-digested nutrients and digestive nutrients seem to be effective, but it may be impossible to administer these in cases involving aggravated symptoms. Further studies should be performed in order to determine the type of enteral nutrient that is most useful.

Radical surgical treatment

CQ5-1: Is radical surgical treatment (other than stoma construction) recommended for the treatment of isolated hypoganglionosis?

Recommendation. Avoidance of radical surgical treatment is proposed (2C = weak recommendation, based on weak evidence).

Enterostomy at an appropriate site for decompression is useful for preventing congestive enteritis. Only one SR has shown that intestinal resection and tapering improved the symptoms of bowel obstruction in isolated hypoganglionosis.[70] Given that peristaltic disorder is observed all over the intestinal tract,[26,70] no recommendations for radical surgery have been established.

CQ5-2: Is radical surgery (other than stoma construction) recommended for the treatment of MMIHS?

Recommendation. The resection of the dilated intestine does not improve the symptoms of ileus in MMIHS; thus, avoidance of radical surgery is proposed (2D = weak recommendation, based on very weak evidence).

There have been no reports of radical surgery improving the symptoms of ileus in MMIHS. Martin-type jejunum side-to-side anastomosis, and additional small intestinal resection and right hemicolectomy failed to improve the symptoms of MMIHS.[48] Resection of the dilated segment did not improve the symptoms of abdominal distension or ileus, and the effectiveness of radical surgery has not been confirmed in the literature.[71]

CQ5-3: Is radical surgery (other than stoma construction) recommended for the treatment of CIIP?

Recommendation. The concomitant use of antegrade continence enema and antidromic enema is suggested to improve defecation in patients with CIIP. In cases of duodenal dilatation, duodenojejunostomy has been suggested to improve the intestinal transit. It may relieve the pseudo-obstructive symptoms to some extent. Intestinal resection does not improve the pseudo-obstructive symptoms; thus, avoidance of radical surgical treatment is proposed (2D = weak recommendation, based on very weak evidence).

Antegrade continence enema was found to remarkably improve defecation, but to only mildly improve abdominal distension.[72] Duodenojejunostomy, in the case of duodenal dilatation, remarkably improved the transit of the dilated intestine, and improved the symptoms to some extent.[73] Ileocecal resection reduced the time taken for contrast medium to reach the colon on imaging.[74] In the meantime, some case reports have shown harmful outcomes of intestinal resection for CIIP. Ileocecal resection and colectomy did not improve the symptoms of bowel obstruction.[75,76] Based on the report of surgery-related death,[53] attempting radical surgery for CIIP would be harmful.

Small bowel transplantation

In Japan, the first small bowel transplantation was performed in 1996, and 26 transplantations (in 23 patients) had been performed by 2014. Postoperative patient survival and graft survival rates at 1, 5, and 10 years were 87%, 68%, 58%; and 80%, 59%, 44%, respectively. The short-term results are relatively good, while the long-term prognosis is still poor.[77]

CQ6-1: Is small bowel transplantation useful for the treatment of isolated hypoganglionosis?

Recommendation. Small bowel transplantation has been proposed for the treatment of isolated hypoganglionosis, given that it may be useful in the following cases: when discontinuation of parenteral nutrition is difficult even after the maximum use of the native intestinal tract under intestinal rehabilitation; when the number of central venous access routes is low; in repeated episodes of sepsis; and in progressive hepatopathy (2D = weak recommendation, based on very weak evidence).

Regarding cases in which small bowel transplantation was performed for hypoganglionosis in Japan, as of January 2016, based on a report from the Japanese Intestinal Transplantation Registry and confirmation by the institutions in which transplantation was performed, nine small bowel transplantations (living donors, $n = 6$; brain-dead donors, $n = 3$) have been performed in eight patients; the patient survival rate was 7/8 (88%), and the graft survival rate was 5/9 (56%). Of the five cases in which graft survival was achieved, complete discontinuation without requirement of transfusion was achieved in 3/5 (60%), and in 2/5 (40%) transfusion was required temporarily or always. Stoma closure was performed in 1/5 cases (20%); partial closure, such as Bishop–Koop and Santulli, was performed in 2/5 (40%); permanent enterostomy was required in 2/5 cases (40%). We should carefully determine the indications for small bowel transplantation as a surgical treatment for isolated hypoganglionosis, and establishment of control by the patient's own intestine should be given the highest priority.[77]

CQ6-2: Is small bowel transplantation useful for MMIHS?

Recommendation. Small bowel transplantation is proposed for cases not involving liver or renal failure complications. Multiple organ transplantation is proposed in the case of liver or renal failure complications (2D) = (weak recommendation, based on very weak evidence).

Small bowel transplantation for MMIHS has never been performed in Japan (as of January 2016). Papers on organ transplantation have been reported only from overseas, and most of the cases involved multiple organ transplantations, given that hepatic failure and renal failure were present at the time of transplantation in the majority of cases.[78–82] Multivisceral transplantation can be performed only overseas, and combined liver/small bowel transplantation is still considered to be difficult to perform in Japan. Thus, isolated small bowel transplantation might be useful when the disease is not complicated by hepatic failure. This is the current situation of small bowel transplantation for MMIHS in Japan.

CQ6-3: Is small bowel transplantation useful for CIIP?

Recommendation. Small bowel transplantation is proposed for the treatment of CIIP given that it may be useful in the following cases: when symptoms remain intolerable even with adequate parenteral nutrition, enteral nutrition, and gastrointestinal decompression therapy; when the number of central venous access routes is low; and for repeated episodes of sepsis. The possible impairment of the native gastric outlet function needs to be considered when small bowel transplantation is planned and performed (2D = weak recommendation, based on very weak evidence).

Given that this disease is often characterized by gastric emptying disorder, multiple organ transplantation, including the stomach, has generally been performed overseas.[83,84] In

Japan, 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. It was difficult, however, to establish oral intake in both cases. Only one of the three patients survived. Small bowel transplantation may be the only treatment for severe CIIP, but is difficult to establish oral intake 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 carefully provided with close consideration of the appropriate anastomosis approach to ensure gastric emptying function in each case.[85]

Prognosis

CQ7-1: What is the prognosis of isolated hypoganglionosis?

Recommendation. Long-term survival can be expected with appropriate treatment. In many cases, adequate nutritional support and intestinal stoma care are required for a long period of time (C = no definite recommendation, based on weak evidence).

The 10 years survival rate for isolated hypoganglionosis patients according to a nationwide survey in Japan was 78% (70/90 patients).[7] In an SR, multidisciplinary treatment improved the survival rate from 12.6% in 1977 to 55.6% in 2011.[86] Patients who receive appropriate therapy can expect longer survival. Of these cases, there were some in which disease control was obtained with oral intake alone, in which normal growth or only mild growth disorder was observed, and in which school attendance was achieved. In many cases, however, long-term management of nutrition, and enterostomy are required.

CQ7-2: What is the prognosis of MMIHS?

Recommendation. Patients with MMIHS has a poor prognosis compared with healthy children, but long-term survival can be expected with appropriate treatment. In many cases, adequate nutritional support and intestinal stoma care are required, and the functional prognosis is poorer than that of healthy children (C = no definite recommendation, based on weak evidence).

The 10 years survival rate for MMIHS patients according to a nationwide survey in Japan was 53% (10/19 patients).[7] Patients with MMIHS, which is the most serious type of disease, present with functional ileus, which has a poor prognosis.[78] The associated causes of death included sepsis, malnutrition, hepatic failure, renal failure, and multiple organ failure.[79,87] The age at death ranged from immediately after birth to 15 years of age; approximately 80% of patients die in infancy (<1 year after birth). Some cases in Japan have shown functional improvement: an infant was successfully self-defecated and self-urinated at 1 year and 10 months of age,[49] and an infant achieved normal intake at 2½ years of age.[88] With regard to the physical and mental development of Japanese children with MMIHS, two reports have described patients starting school under home parenteral nutrition.[89,90]

CQ7-3: What is the prognosis of CIIP?

Recommendation. The actual prognosis of CIIP that develops in childhood is not poor, but adequate nutritional support and intestinal stoma care are required for a long period in many cases. The functional prognosis of CIIP is poor (C = no definite recommendation, based on weak evidence).

The 10 years survival rate for CIIP patients according to a nationwide survey in Japan was 89% (50/56 patients).[7] In Japan, the prognosis of childhood CIIP seems to be relatively good.[36] In clinical practice, repeated hospitalization is sometimes required for CIIP due to the exacerbation of pseudo-obstructive symptoms. Even for outpatients, the requirement of i.v. nutritional support and enterostomy itself may significantly limit daily life. Although the prognosis of CIIP with respect to survival is good, this outcome is deemed unsatisfactory because it may have a long-term impact on quality of daily life.[91]

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Disclosure

The authors declare no conflict of interest.

Author contributions

The individual author contributions to the establishment of the guidelines and the author affiliations are listed in Table S1.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Development organization.