Clinical and surgical aspects of Hirschsprung's disease

Daisy Schulten-Vieira Travassos

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Clinical and surgical aspects of Hirschsprung's disease

Klinische en chirurgische aspecten van de ziekte van Hirschsprung

(met een samenvatting in het Nederlands)

Klinische und chirurgische Aspekte des Morbus Hirschsprung

(mit einer Zusammenfassung in deutscher Sprache)

Proefschrift

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Daisy Schulten - Vieira Travassos

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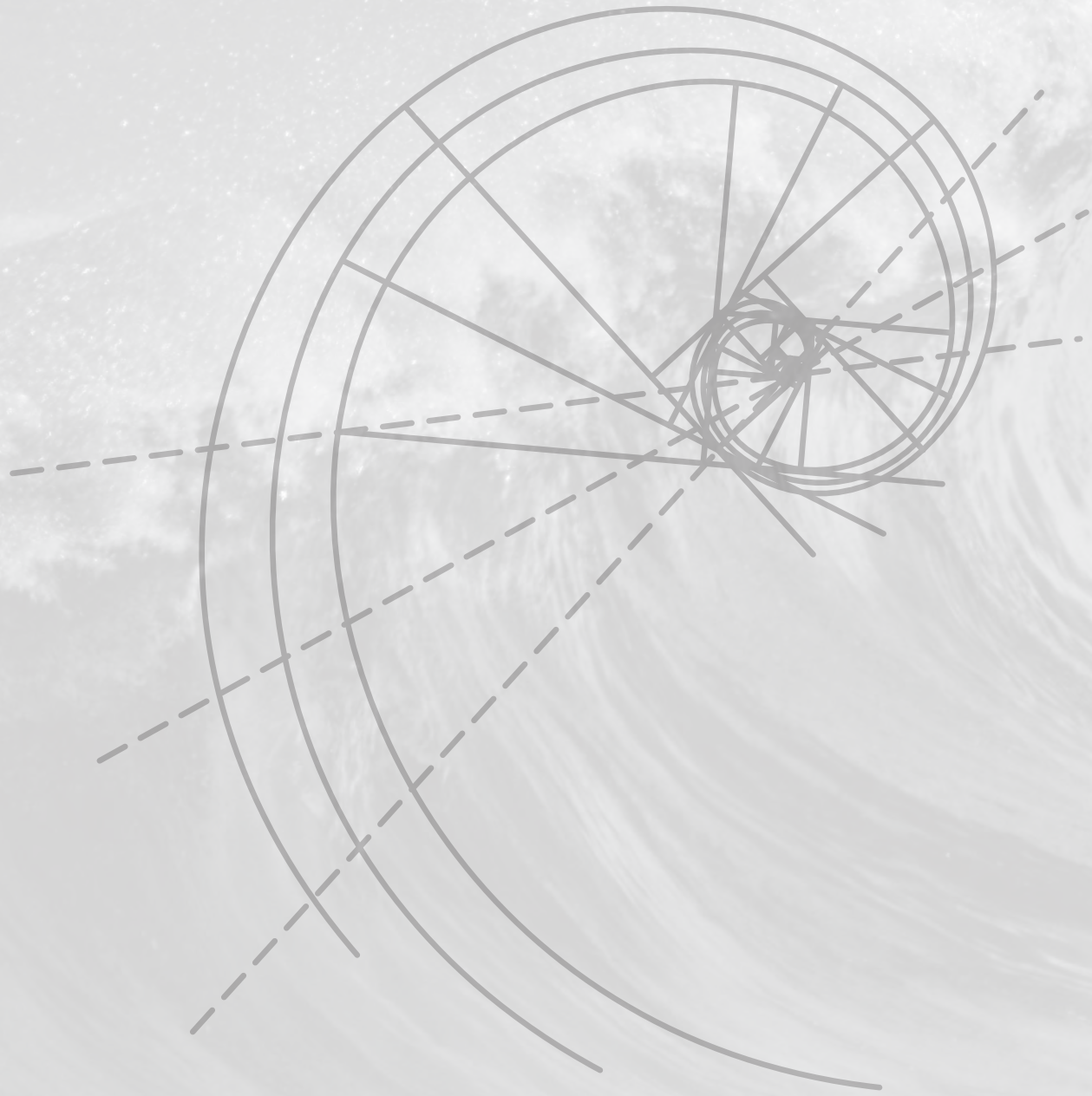
Prof. dr. B.M. Ure

Contents



Chapter 1

Introduction

Hirschsprung's disease is is an important topic, frequently seen in pediatric surgery. It is an important cause of intestinal obstruction or constipation in newborns and children. It is characterized by the lack of ganglion cells, caused by arrest of migration of the ganglion cells from the neural crest. The lack of ganglion cells extends from the internal anal sphincter up to more proximally in the colon or even small bowel. In 80% of the cases the aganglionosis involves the rectosigmoid colon, in 11 to 26% the left colon, and in 5 to 15% the entire colon. [1]. The incidence is estimated to be one in 5,000 newborns, but varies between the racial groups. There is a male to female predominance of about 4:1, which is less evident in patients with long segment aganglionosis and Down syndrome. Hirschprung's disease presents itself mostly sporadic, however in about 20% a genetic inheritance is present.[1]

Approximately 30% of the affected patients show an association with other disorders or chromosomal anomalies. Patients with Down syndrome have a five percent higher risk to be affected by Hirschsprung's disease than the general population.[1]

The proto-oncogene RET is the gene most frequently responsible for Hirschsprung's disease. RET mutations are also implied in other pathologies, such as multiple endocrine neoplasia of type 2A (MEN 2A), 2B (MEN 2B) and medullary thyroid carcinoma, both sporadic (MTC) and familial (FMTC).[1]

1.1 History of Hirschsprung's disease

Harald Hirschsprung, a Danish pediatrician presented the most informative description of Hirschsprung's disease in 1886 at the Society of Pediatrics in Berlin. He believed that the symptoms of constipation were caused by the dilated and hypertrophied colon. He neither speculated the etiology nor suggested a treatment for the disease. In the next decades, many case reports of Hirschsprung's disease were published mostly based on autopsy findings.[1] Despite that in 1920 Dalla Valla reported the absence of ganglion cells in the sigmoid colon in two brothers who had normal ganglion cells in the proximal colon, the origin of the innervation anomaly remained unclear.[1] Ehrenpreis first considered the loss of the ganglion cells as a secondary event because of the persistent colonic dilatation and stasis.[1]

As long as the unawareness of the pathology of the colonic innervation persisted, it remained difficult to propose a single effective treatment.

The treatment in those days was in fact quite diverse, ranging from lumbar sympathectomy (1927, Wade and Royle), administration of parasympathomimetic drugs (1930, 1940) to segmental resection of the dilated colon and colostomy.[1]
In 1948, Swenson, performed a life-saving colostomy in his patients with relieve of the obstructive symptoms that recurred after closure of the colostomy. This observation led him to resect the colon from a point proximal to the abnormal area downwards and perform a coloanal anastomosis above the dentate line. This was the first successful operative procedure for Hirschsprung's disease. [1]
Although Swenson's operation had proven to be effective, many other surgeons had less favourable results or considered the operating-time being too long. In search for other operative techniques, several surgeons around the world proposed different methods which are still being used: The retrorectal transanal pull-through of Duhamel (1956), the deep anterior resection of Rehbein (1958), the endorectal pull-through of Soave (1963) and endorectal pull-through of Rintala and Lindahl (1993). With the introduction of laparoscopy in the 1990's, most of the former open techniques were modified into laparoscopic ones. The laparoscopic endorectal pull-through is gaining popularity around the world, while most of the other techniques are still being performed.

1.2 Diagnosis of Hirschsprung's disease

Clinical presentation

Hirschsprung's disease should be suspected in any newborn that presents with constipation and/or failure to pass meconium within 48 hours of life. This symptom may be absent in 6% to 42% of the patients. [4] Other symptoms besides constipation can be signs of low intestinal obstruction such as abdominal distension and bilious vomiting. Hirschsprung's disease can also first present it self as enterocolitis and sepsis, mainly in the more extended forms. After the newborn period, the most common presentation is constipation, abdominal distention accompanied with failure to thrive.

Radiological diagnosis

Contrast enema.
The classic radiographic finding of a contrast enema in Hirschsprung's

disease is a spastic, narrow bowel segment distally extending into a distended bowel segment proximally. Unfortunately, not all the patients presenting with Hirschsprung's disease can be diagnosed by contrast enema. The mean specificity and sensitivity are, respectively 83% and 70% according to the study published by Benninga et al. [5]. In total colonic aganglionosis, a radiological diagnosis is more difficult because the transition zone from the narrow to the dilated caliber may be absent. There are three different radiological patterns described in total colonic aganglionosis: microcolon-shape (24%), normal-shape (53%) and question-mark shape (18%). [6]

Transit-time studies:
Transit-time studies are useful to estimate the length and level of involved bowel segment in patients with chronic constipation and intestinal motility disorders. Holschneider used a modification of the method of Hinton et al. [4] Twenty radiopaque pellets are swallowed by the patient and the position of the markers or their disappearance from the gut is monitored by serial radiographs at 24 hours interval. Six hours after ingestion the markers can be demonstrated at the ascending colon and after 48 hours, 80% of the pellets should be passed. The pellets can also be introduced in the aboral part of the stoma to determine the function of the distal intestine before closing the stoma.

Functional diagnosis: anorectal manometry

Normally, an increase in the pressure in the rectal lumen results in internal sphincter relaxation. In Hirschsprung's disease this reflex is absent. Unfortunately, the reliability of anorectal manometry is limited in newborns; while this is the age that the most of the children suspected for Hirschsprung's disease should undergo a diagnostic manometry. The accuracy rate of anorectal manometry in Hirschsprung's disease varies between the different authors. The false negative rate varies from 0% to 24% and the false positive rate ranges from 0% to 62%. [4] The mean specificity and sensitivity are, respectively 83% and 70% according to the study published by Benninga et al. [5].

Histopathological diagnosis

The histopathological diagnosis is the most accurate method for the diagnosis of Hirschsprung's disease and is the gold standard.
The main finding in Hirschsprung's disease is the lack of ganglion cells in the narrow segment of the colon. The aganglionic segment starts distally at the anal ring and extends proximally to a variable length.
The internal sphincter has a natural scarcity of ganglion cell close to the anus for a length about 10mm above the dentate line. That is the reason for the general rule to perform biopsies 2-3 cm above the dentate line.[4]
The biopsies can be obtained by full thickness biopsy under general anesthesia or by suction biopsy (mucosal-submucosal) at the bedside. With the advance of enzyme histochemistry, that allows an easier and reliable diagnosis with small amounts of tissue, the suction rectal biopsy is now the first choice. However in selected cases, when the diagnosis cannot be made by suction biopsy, a full thickness biopsy is still usefull. The diagnostic accuracy of the suction rectal biopsy is 99,7%. [4]

Histopathological techniques

Besides the traditional staining method with hematoxylin and eosin (H&E), a number of histochemical staining methods are very useful and have been used in the histopathological diagnosis of the gastrointestinal tract. Acetylcholinesterase (AChE), the most often used staining technique, shows cholinergic structures and demonstrates parasympathetic activity of muscularis propria. [7] Lactic dehydrogenase (LDH) is an unspecific marker of cytoplasm in mature nerve cells. Succinic dehydrogenase (SDH) is a good marker for mitochondria in mature nerve cells. [7] Nitroxide synthase (NOS) is a nonspecific cytoplasmic nerve cell marker, irrespective of nerve cell maturity. [7]
Meier-Ruge did extensive research regarding the histopathological diagnosis of Hirschsprung's disease and other congenital neuronal intestinal malformations [4] describing the following criteria:

- *Hirschsprung's disease:*
  is characterized by absence of nerve cells in the submucous and myenteric plexus and by the increase in AChE activity in the parasympathetic nerve fibers of the lamina propria mucosae.

- *Total aganglionosis of the colon:*
  is characterized by absence of nerve cells in the submucous and myenteric plexus, but the AChE activity is less accentuated than in classical segment Hirschsprung's disease, because total aganglionosis is consistently associated with moderate hypoplasia of the extramural parasympathetic innervation.

- *Hypoganglionosis:*
  hypoganglionosis as an isolated malformation occurs in only 5% of intestinal malformations. It may occur proximal to the aganglionic bowel segment in Hirschsprung's disease (transitional zone) and may be one of the causes of postoperative constipation after resection of the aganglionic bowel. The histopathological diagnosis of hypoganglionosis is suggested by a low level of AChE activity and a scarcely developed submucous plexus in the suction biopsy but, can only be proven by full thickness or a seromuscular biopsy, which allows the examination of the myenteric plexus, a prerequisite for a reliable diagnosis of hypoganglionosis.

- *Neuronal Intestinal Dysplasia Type B (NID):*
  intestinal neuronal dysplasia is a developmental abnormality of the submucous plexus. The most characteristic findings are giant ganglia in the submucosa with more than eight nerve cells. Meier-Ruge first described this condition in 1971 [2,3]. The criteria for NID are 15-20% submucosal giant ganglia with more than eight nerve cells in 30 sections of a single biopsy [8].

  Intestinal neuronal disorders can present isolated or in association with Hirschsprung's disease. When associated with Hirschsprung's disease and not fully resected with the aganglionic segment, symptoms may persist. Isolated NID B can be a cause for constipation in children but the management is mostly conservative.

1.3 Aim/background and outline of this thesis

There is diversity in operative techniques, which is a sign that the ideal operative method has not been invented yet. Independent of the operative method, the reason why some patients do present poor results and others do not after operative treatment for Hirschsprung's

disease, still remains unclear. Among others, associated intestinal neuronal malformations may play a role in surgical outcome. Operative techniques have changed over the years and insight in subgroups may give new ideas on optimal treatment. In this thesis, data are analyzed taking several aspects of Hirschsprung into account such as: extension of the aganglionosis, association with Down's syndrome, associated neuronal intestinal malformations and the open versus laparoscopic approach.

Chapter 2: 141 patients diagnosed with intestinal neuronal malformations were analyzed. The diagnosis included aganglionosis, intestinal neuronal dysplasia, hypoganglionosis, immaturity of the ganglion cells, reduced parasympathetic tone, heterotopia of the submucous plexus, heterotopia of the myenteric plexus and mild dysganglionosis. The impact of symptoms and kind of therapy required (operative or conservative) of the patients presenting intestinal neuronal malformations (IND) and aganglionosis, were reported.

Chapter 3: Transit time studies were performed in 106 children diagnosed with different types of neuronal intestinal malformations and a correlation was established between the type of intestinal neuronal malformation and the transit time findings. A link between the children that required operative treatment and their transit time findings was observed.

Chapter 4: The proximal segment histology of the resected bowel from 101 patients operated for Hirschsprung's disease by the Rehbein procedure at the Children's Hospital, Cologne, Germany, was analyzed and the findings correlated to the postoperative bowel function.

Chapter 5: Presents a comparative study between patients submitted to an open Duhamel procedure (N=25) and patients submitted to a laparoscopic Duhamel procedure (N=30) at the Wilhelmina Children's Hospital, Utrecht. To achieve homogeneity between the two groups, patients with extended aganglionosis, pre- Duhamel stomy or

syndrome were excluded. End points were intraoperative complications, postoperative complications, time to first feeding, hospital stay, and surgical outcome at follow up.

Chapter 6: Among 149 children operated for Hischsprung's disease between 1987 and 2008 at the Wilhelmina Children's Hospital, Utrecht, 20 were additionally diagnosed with Down syndrome.
The postoperative complications and outcome of patients, with Down syndrome (DS) were compared to patients without Down syndrome (NDS).

Chapter 7: Over a period of 22 years 163 children with Hirschsprung's disease were operated in the Wilhelmina Children's Hospital, Utrecht. Fifteen children had total colonic aganglionosis. The outcome of the total aganglionosis cases were analyzed concerning postoperative complications, mortality rate and symptoms at follow up. Three special cases of extended total aganglionosis up to the middle ileum were presented in which aganglionic ileum was left in situ, which up to now has been contradictory to the conventional rule to resect the entire aganglionic bowel as the operative treatment for Hirschsprung's disease.

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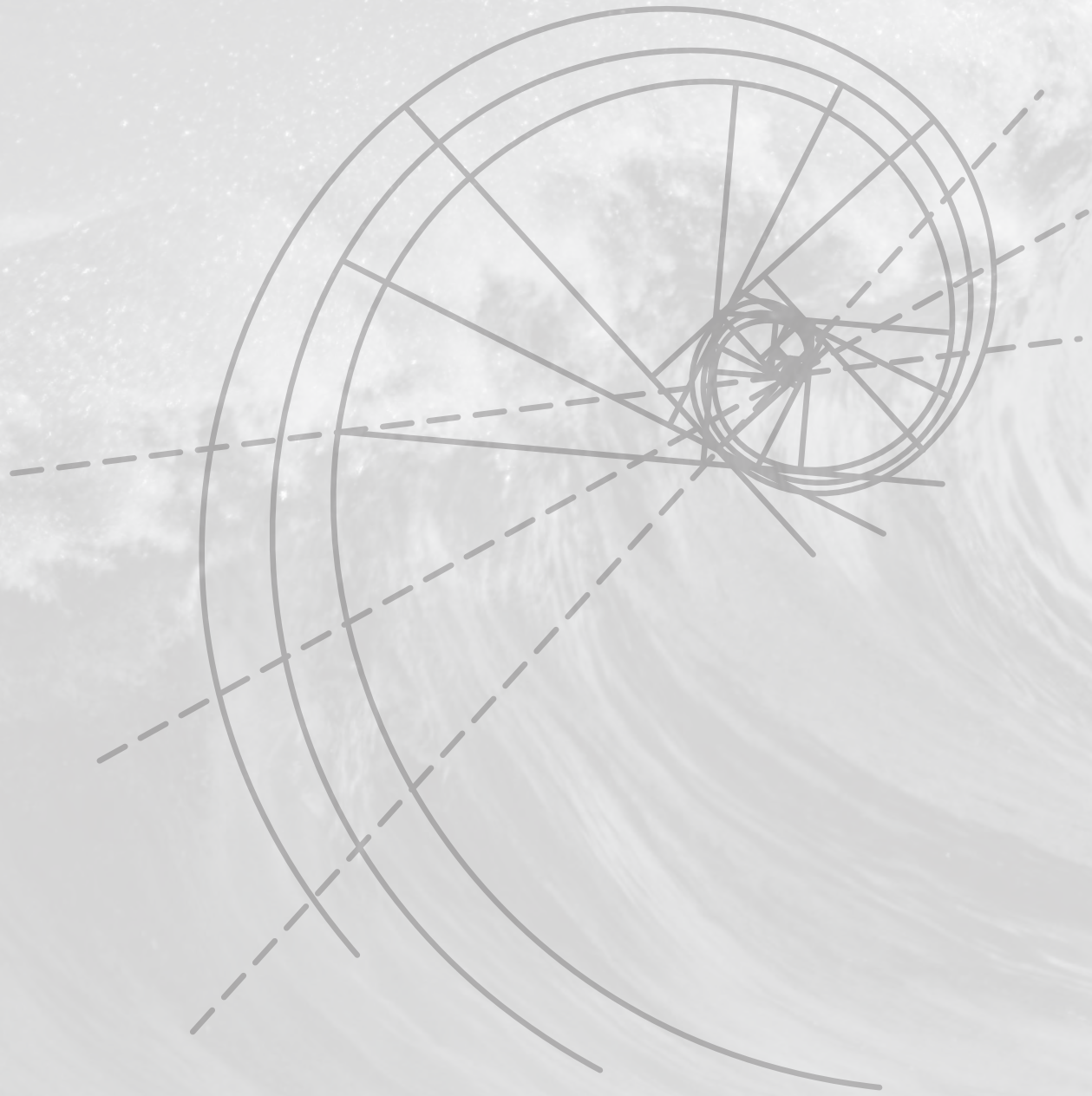

Chapter

2

Clinical impact of intestinal neuronal malformations: a prospective study in 141 patients

B. M. Ure[1], A. M. Holschneider[1], D. Schulten[1], W. Meier-Ruge[2]

[1]Department of Pediatric Surgery, The Children's Hospital of Cologne, Germany
[2]Department of Pathology, University of Basle, Switzerland

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Abstract

A prospective study of 141 consecutive patients with intestinal neuronal malformations is presented. The single malformation of the autonomic nervous system that always required surgical intervention was aganglionosis. Giant ganglia, reduced parasympathetic tone, immature ganglia, and hypogenetic or heterotopic nerve cells were seen in all forms of malformations. However, the incidence in specific malformations was variable. Multiple giant ganglia were identified in all patients with intestinal neuronal dysplasia (IND) type B, but also in various other malformations. Heterotopic nerve cells in the myenteric plexus were seen in the proximal segment of 15 of 74 patients (20.3%) with aganglionosis and 5 of 9 patients (55.6%) with hypoganglionosis. A significant impact on symptoms was found for IND type B: 34 (45.9%) of 74 children with aganglionosis had associated IND type B, and these children more frequently developed ileus ($P < 0.001$) and more often needed a second resection ($P < 0.05$) compared to those with isolated aganglionosis. This indicates an additive effect of both malformations, and therefore, in these patients an extended resection should be carried out.

Twelve of 67 patients (17.9%) without aganglionosis needed resection for untreatable constipation. This included 7 of 9 children with hypoganglionosis, both patients with heterotopia of the myenteric plexus, 1 of 20 with isolated IND type B, and 2 of 12 with reduced parasympathetic tone. None of the patients with immaturity, heterotopia of the submucous plexus, or mild dysganglionosis required surgery. Six children (8.9%) without aganglionosis underwent sphincteromyotomy and 2 with IND type B had a temporary colostomy. At follow-up (mean 2.4 ± 1.4 years), the outcome in patients with resected aganglionosis was better than in patients who had resections for other malformations; 49 (69%) of 71 patients with aganglionosis were asymptomatic compared to 4 (33.3%) of 12 with other malformations ($P < 0.05$). It is concluded that some intestinal malformations have a relevant clinical impact. However, the severity of symptoms in the individual patient may not be explained by specific histochemical findings from a limited number of mucosal biopsies. The pathognomonic histochemical criteria of isolated IND type B - immaturity, reduced parasympathetic tone, heterotopia of the submucous plexus, and mild dysganglionosis - rarely require surgical therapy and should be treated conservatively.

Introduction

Since the first report of a case of intestinal neuronal dysplasia (IND) by Meier-Ruge in 1971 [1] numerous reports of intestinal neuronal malformations have been published [2-4]. Some of these malformations are now well known, but their definition is still a topic of debate. In addition, there is ongoing discussion about the causal relationship between specific histochemical abnormalities and clinical symptoms [2, 3, 5]. The aim of the present study was to determine specific histochemical findings in a consecutive series of patients and to investigate the impact of these findings on the symptoms, surgical therapy, and long-term results.

Patients and methods

From November 1989 to July 1995, 141 consecutive patients with intestinal neuronal malformations were included in a prospective study. The mean age at diagnosis was 4.5 ± 5.2 years; 98 patients (69.5%) were male and 43 (30.5%) female. Urogenital, cardiac, or orthopedic malformations were present in 12 patients (8.5%); 9 (6.4%) had trisomy 21. Children with additional malformations of the bowel such as imperforate anus (n = 54), small-bowel atresia (n = 18), and necrotizing enterocolitis (n = 5) were excluded from the study. Another patient with aganglionosis was excluded after the parents had refused any therapy.

Preoperative assessment was performed according to a protocol that has been published previously [6]. All children and/or parents were interviewed and specific symptoms such as constipation, overflow incontinence, enterocolitis, and occasional ileus were recorded. Constipation was defined as stool retention for at least 5 days, enterocolitis as diarrhea or abdominal distension that required hospital admission. In a subgroup of patients electromanometry, an X-ray contrast enema examination, and transit time studies were performed. The methods and a preliminary report on the results of these studies have been published recently [6] and are excluded from the present analysis.

Suction biopsies were taken according to the method of Noblett[7], and specimens were processed as suggested by Meier-Ruge et al. [8]. Biopsies and specimens were investigated by the Institute of Pathology of the University of Basle, Switzerland. The histochemical methods

used for the identification of autonomic innervations patterns have been published by Meier-Ruge et al. [4, 8]. Parasympathic fibers were identified by acetylcholinesterase (AChE) staining. Nerve cells of the submucous plexus were selectively visualized by a lactic dehydrogenase (LDH) reaction. The succinic dehydrogenase (SDH) reaction allowed mature, fully-developed cells to be distinguished from immature cells.
Intestinal malformations were classified according to the results of the consensus conference of Borchert et al. in 1990 [2] such as aganglionosis, IND types A and B, and hypoganglionosis. IND type B was characterized by a high number of giant ganglia in the submucous plexus containing more than 7 LDH-positive nerve cells and immaturity or hypogenesis of the submucous plexus [9]. Hypoganglionosis was diagnosed when a very low level of AChE activity in the mucosa combined with a significant deficiency of nerve cells in the myenteric plexus was found. In addition, a heterogeneous group of not-yet-classified dysganglionoses such as immature ganglia or hypogenetic nerve cells, reduced parasympathetic tone, heterotopic nerve cells in the submucous or myenteric plexus, and mild dysganglionosis were defined according to Meier-Ruge et al. [4, 8, 9] Conservative treatment and operative procedures such as Rehbein's anterior resection, temporary colostomy or ileostomy, and sphincteromyotomy were recorded. All patients underwent follow-up for a mean of 2.4 ± 1.4 years and follow-up symptoms were assessed as they were preoperatively. Normal bowel function was defined as sufficient bowel movements without laxatives, enemas, or other conservative measures. The biomedical data package PC-90 (BMDP Statistical Software, Cork, Ireland) was used for statistical analysis. Univariate analysis was carried out by the Wilcoxon rank-sum test and Fisher's exact test. A *P* value of less than 0.05 was considered significant.

Results

Histochemical findings

Aganglionosis was found in 74 patients (52.5%); 40 (54%) had classic aganglionosis and in 34 (46%) additional IND type B was identified in the proximal bowel segment. Hypoganglionosis proximal to the aganglionic segment was seen in 47 (63.5%) patients, heterotopic nerve cells in the myenteric plexus in 15 (20.3%). Intestinal malformations without aganglionosis were present in 67 patients (47.5%). Of these, 20 (29.8%)

had isolated IND type B and another 16 (23.9%) isolated heterotopia of the submucous plexus. All other malformations such as hypoganglionosis, reduced parasympathetic tone, heterotopia of the myenteric plexus, and mild dysganglionosis were found in less than 10% of the patients of the whole series (Table 1).

An aganglionic segment was pathognomonic for Hirschsprung's disease (HD). Other findings such as giant ganglia, immature ganglia or hypogenetic nerve cells, reduced parasympathetic tone, heterotopic nerve cells in the submucous plexus, and mild dysganglionosis were found in the bowel proximal to an aganglionic segment as well as in all other isolated forms of intestinal malformations. However, the incidence varied according to specific malformations. In all patients with IND type B a high number of giant ganglia was identified in the submucous plexus, but some giant ganglia were also found in 4 patients with hypoganglionosis, 1 with immaturity, 2 with reduced parasympathetic tone, 2 with heterotopias of the submucous or myenteric plexus, and 1 with mild dysganglionosis. Isolated heterotopic nerve cells in the myenteric plexus were diagnosed in 2 patients, but were also found in the proximal segment of 15 patients (20.3%) with aganglionosis and in 5 patients (55.6%) with hypoganglionosis.

Preoperative symptoms

In 83 patients (58.9%) constipation was the main symptom that led to presentation. Ileus was present in 43 children (30.5%). Twenty-five of the 34 patients (73.5 %) in whom aganglionosis was combined with IND type B had an ileus, compared to only 13 of 40 patients (32.5%) with classic aganglionosis ($P < 0.001$, Fig. 1). Two additional patients with IND type B, 1 with hypoganglionosis, and 1 with heterotopia of the submucous and myenteric plexuses presented with ileus, but none with immaturity, reduced parasympathetic tone, or mild dysganglionosis. Further symptoms were overflow incontinence in 6 (4.2%) and enterocolitis in 9 patients (6.4%).

Therapy

All patients with aganglionosis underwent resection and subsequent colostomy closure if present. Seven of these children (9.6%) needed a second resection because of untreatable constipation; 6 of these 7 had

aganglionosis combined with IND type B and 1 had isolated aganglionosis. The difference in the frequency of a second resection was significant ($P < 0.05$). In 4 of these patients the first resection had not been performed in our clinic.

Conservative treatment was performed in 47 (70.1%) of the 67 patients without aganglionosis (Fig. 2). Twelve of these patients (17.9%) underwent resection because of severe constipation; in 6 of these children long-term conservative treatment had failed. Seven of the children with resections had hypoganglionosis, 1 IND type B, 2 reduced parasympathetic tone, and 2 heterotopia of the myenteric plexus. Three of these patients needed a second resection; 1 had IND type B, 2 hypoganglionosis. No patient with immaturity, heterotopia of the submucous plexus, or mild dysganglionosis underwent a resection. Two patients with IND type B had a colostomy that was subsequently closed without further resection. In 6 (8.9%) of the patients without aganglionosis a sphincteromyotomy was done.

Findings at follow-up

Four patients, 3 with aganglionosis and 1 with hypoganglionosis, died within the study period, 1 from enterocolitis and sepsis. In 3 children the cause of death was not related to intestinal malformations or surgical therapy. At follow-up 2.4 ± 1.4 years after the initial therapy, 49 of 71 patients (69%) who underwent resection of an aganglionic bowel segment had normal bowel movements and were free of symptoms. There was no significant difference in the percentage of patients with classic aganglionosis who were asymptomatic compared to those with aganglionosis combined with IND type B. Of 66 patients without aganglionosis, 29 (43.9%) were asymptomatic at follow-up (Fig. 3). Of the 12 children who underwent resections, 4 (33.3%) had normal bowel movements, significantly less than the 69% of patients with resections for aganglionosis ($P > 0.05$). This was due to the unfavorable results in patients with hypoganglionosis in whom parts of the hypoganglionic colon had been left in place in order to avoid total colonic resection and ileorectostomy. At follow-up 4 of the 9 children with hypoganglionosis had constipation and 1 had overflow encopresis. These symptoms were successfully managed by conservative treatment. Of the 54 patients without aganglionosis who had undergone conservative treatment, sphincteromyotomy, or closure of a colostomy, 25 (46.3%) were free of

symptoms at follow-up. Twenty (37%) had persistent constipation, 7 (13 %) overflow incontinence, and 2 (4%) enterocolitis. All 29 patients with symptoms were willing to tolerate their complaints and stated that symptoms had improved since the initial treatment.

Discussion

There is no universally accepted technique for the investigation of intestinal neuronal malformations. However, the consensus conference of Borchard et al. in 1990 [2] tried to overcome this inconsistency, and since then the preferred enzymehistochemical methods were reported in a series of publications. Meier-Ruge et al. [4, 9], Schärli [10], and Holschneider et al. [3] recommended AChE, LDH, and SDH reactions. Various other staining procedures such as S-100 protein, immunhisto–chemistry for PGP 9.5, and other glial and neuronal markers have been applied with success [11], but are not generally accepted for routine use [3, 10, 12] because of the strong variability of their reactions. Therefore, AChE, LDH, and SDH staining techniques were used exclusively in the present study. There is unanimous agreement that classic aganglionosis is enzymehistochemically characterized by the absence of nerve cells in the submucous and myenteric plexuses and a typical increase in AChE activity. According to Meier-Ruge [4], the diagnosis is characterized by a “yes” or “no” increase in AChE activity. Goto and Ikeda [13] found in a series of 30 children that the proximal extension of increased AChE activity increased with the age at the time of resection and the intensity of AChE activity in rectal suction biopsies. In contrast, the morphologic evidence of specific intestinal neuronal malformations without aganglionosis is still under debate. Although they have been well described [8], pathognomonic criteria are not generally accepted. In children with IND type B, Meier-Ruge et al. [8, 9] reported significantly increased numbers of nerve cells per ganglion and size of ganglia in the submucous plexus compared to normal controls. An increased number of giant ganglia with more than 7 LDH-positive nerve cells has been postulated to be typical for IND type B [4], and was found in all patients with this histochemical diagnosis in the present study. Kobayashi et al. [14] found hyperplastic ganglia in all of their IND type B patients, but identified no giant ganglia in four out of nine cases. Two had normal AChE activity and four had ectopic ganglion cells. However, the authors

had used conventional hematoxilin and eosin staining and AChE histochemistry, which is not appropriate for a reliable diagnosis [9]. Therefore, their findings cannot be compared to the present study. The additional use of LDH and SDH reactions and performing 120-160 sections per biopsy [8] seem to be essential in establishing the diagnosis. In the present analysis, aganglionosis was pathognomonic for HD. Other enzymehistochemical findings such as giant ganglia, reduced parasym–pathetic tone, immaturity, hypogenesis, and heterotopic nerve cells were seen in all intestinal malformations. The frequency of these findings varied according to the underlying diagnosis, and therefore, different patterns of histochemical findings were seen. Specific enzymehisto–chemical findings have also been identified in normal colon. Kobayashi et al. [14] found a slight increase in AChE activity in 4 of 23 specimens of normal colon, giant ganglia in 2, hyperganglionosis in 3, and ectopic ganglion cells in another 2. As the histochemical patterns of IND change with age, age-dependent criteria for IND have been suggested [4, 9]. The epidemiology of intestinal malformations has been analyzed by Meier-Ruge [4], and our findings correspond well with this report. However, studies of the sequelae of specific malformations are rare [6, 14-21] and have mainly focused on IND type B. Aganglionosis has been found combined with IND type B in 20%-75% of patients [6, 10, 15-18], in the present series in 46% of the resected specimens. Those children suffered significantly more frequently from ileus. Due to similar findings, Briner et al. [15] suspected a superposition of symptoms. However, Hanimann et al. [18] found no significant difference in early and late complications or results of 5 years' follow-up after the Duhamel procedure in 36 patients with isolated aganglionosis and 11 with associated IND type B. In none of the latter patients had the dysplastic neuronal segment been resected. In our series, patients underwent a Rehbein anterior resec–tion, and a second resection had to be performed in 3 of the 71 patients with aganglionosis who were primarily operated upon by us. Four additional re-resected patients had had primary surgery in other departments. These numbers are too small to compare the techniques of resection, but re-resection was performed significantly more frequently when aganglionosis was associated with IND type B. Therefore, it appears that children with aganglionosis and IND type B should undergo a more extended resection. Varying degrees of severity of symptoms and histochemical involvement have been reported in intestinal malformations without aganglionosis. Munakata et al. [20] found severe constipation

requiring resection in 5 of 9 patients with IND type B; 3 patients died. Schärli [10] performed a posterior sphincteromyotomy in 59% of 22 children with IND, none of whom underwentresection, and achieved a cure in 90% within 3 months. In the present series 25% underwent surgery, only 1 of 20 underwent resection, and 2 received a temporary enterostomy. At follow-up 10 patients had symptoms, and all were successfully managed by conservative treatment. Therefore, long-term maturation may be expected in patients with IND type B. This is supported by the findings of Kaiser et al. [22], who reported a patient with IND of the colon, small bowel, and stomach who had improvement of symptoms 3 years after a temporary colostomy, but there was no change in the histologic pattern. In contrast, Simpser et al. [23] documented one patient with normalization of biopsy findings after 5 years. Schärli [10] reported that among 7 patients with ganglion-cell hypogenesis, 4 needed surgery. In our series hypogenesis was identified in numerous specimens, but never represented the main histochemical diagnosis. Of 13 patients with heterotopia of the submucous plexus and associated IND type B in Schärli's series, 12 were operated upon. However, Meier-Ruge [4] stated that heterotopia of the submucous plexus is extremely common and seems to be a normal variant. In our own series, only 1 out of 12 children with this finding needed a sphincteromyotomy, and 11 underwent successful conservative treatment. Koletzko et al. [19] investigated 6 children with IND type B, 18 with "abortive" IND with heterotopic ganglion cells without hyperganglionosis, and 22 normal controls. The mean colonic transit time and clinical outcome did not differ significantly between the groups. Some histochemical findings such as hypoganglionosis and heterotopia of the myenteric plexus are known to cause severe symptoms [6, 21]. In the present study 9 of 11 children with these diagnoses needed resection, and only 4 were free of symptoms at follow-up. These unfavourable results in patients with hypoganglionosis are due to the fact that we prefer to leave a hypoganglionic colon segment in place to avoid ileorectostomy. The present study indicates that reduced parasympathetic tone in the rectal mucosal biopsy is only a functional indicator that may disappear with maturation of the autonomic nervous system, but may also be indicative of another anomaly of the myenteric plexus. Immaturity of the submucous plexus is due to developmental retardation of the maturation of the nerve cells, which may be bioptically monitored over time. Immaturity of the submucous plexus does not require surgical intervention. Heterotopia of

the submucous plexus and mild dysganglionosis are normal variants that only indicate that the development of the autonomic gut innervations was slightly altered. These cases rarely need surgical treatment. In conclusion, the diagnosis of immaturity, reduced parasympathetic tone, and heterotopia of the submucous plexus indicate that spontaneous improvement may be expected under conservative therapy as a result of the normal development of the child.

Table 1 Histochemical findings in 141 patients with intestinal neuronal malformations diagnosed 1989-1995 (IND intestinal neuronal dysplasia).

Malformation	**n**	**[%]**
Aganglionosis		
Isolated	40	28.4
With IND type B	34	24.1
IND type B	20	14.2
Hypoganglionosis	9	6.4
Other malformations		
Immaturity	4	2.8
Reduced parasympathetic tone	12	8.5
Heterotopia of the submucous plexus	16	11.3
Heterotopia of the myenteric plexus	2	1.4
Mild dysganglionosis	4	2.8

Fig. 1 Leading symptoms in 141 patients: constipation stool retention for at least 5 days; other symptoms overflow incontinence and enterocolitis (AG aganglionosis, IND intestinal neuronal dysplasia type B, HG hypoganglionosis of myenteric plexus, Other malformations: immaturity, reduced parasympathetic tone, heterotopia of submucous or myenteric plexus, mild dysganglionosis).

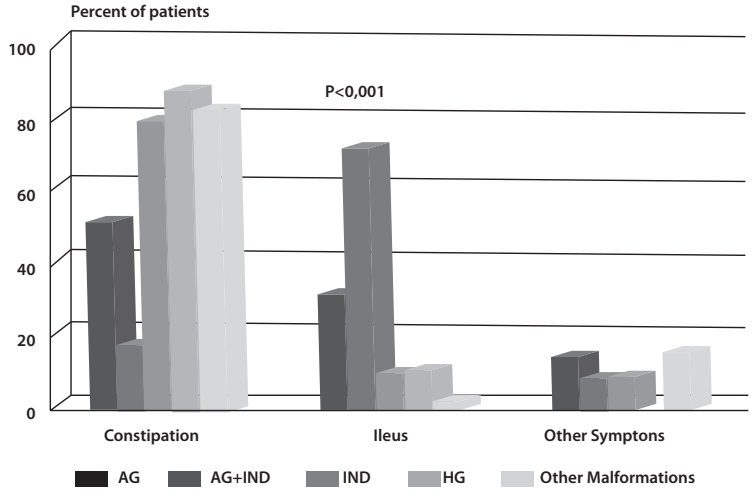


Fig. 2 Therapy in patients with intestinal neuronal malformations without aganglionosis (IND intestinal neuronal dysplasia type B, MP myenteric plexus, SP submucous plexus, Parasympat. parasympathetic tone).

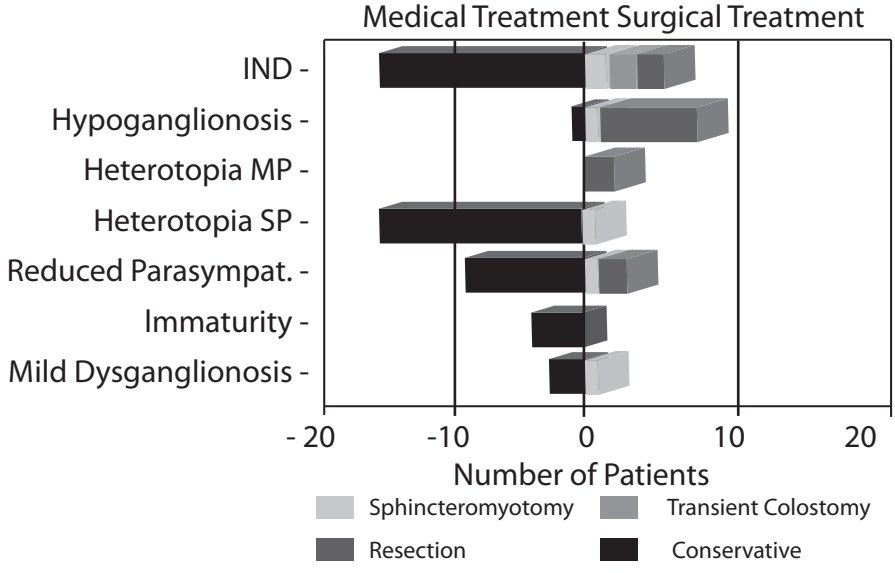
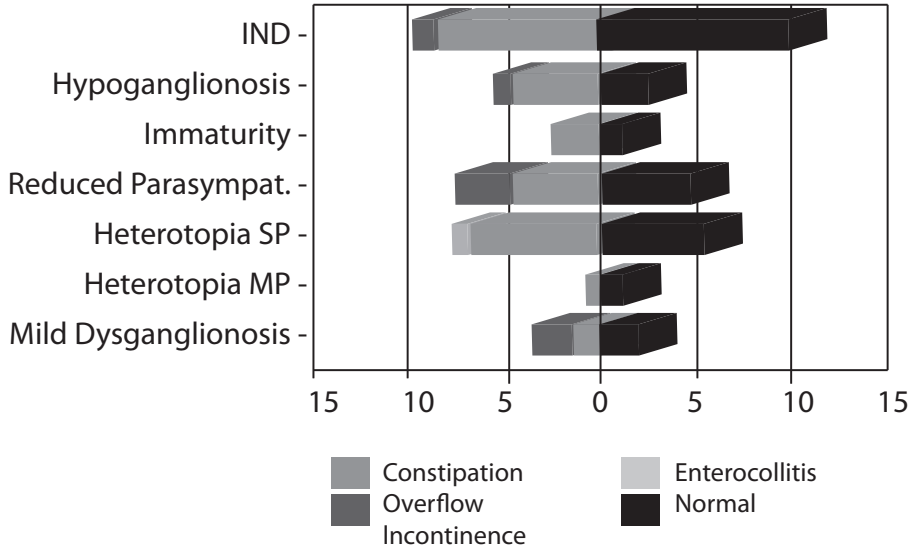


Fig. 3 Results in patients with intestinal neuronal malformations without aganglionosis (IND intestinal neuronal dysplasia type B, SP submucous plexus, MP myenteric plexus, Parasympat. parasympathetic tone).



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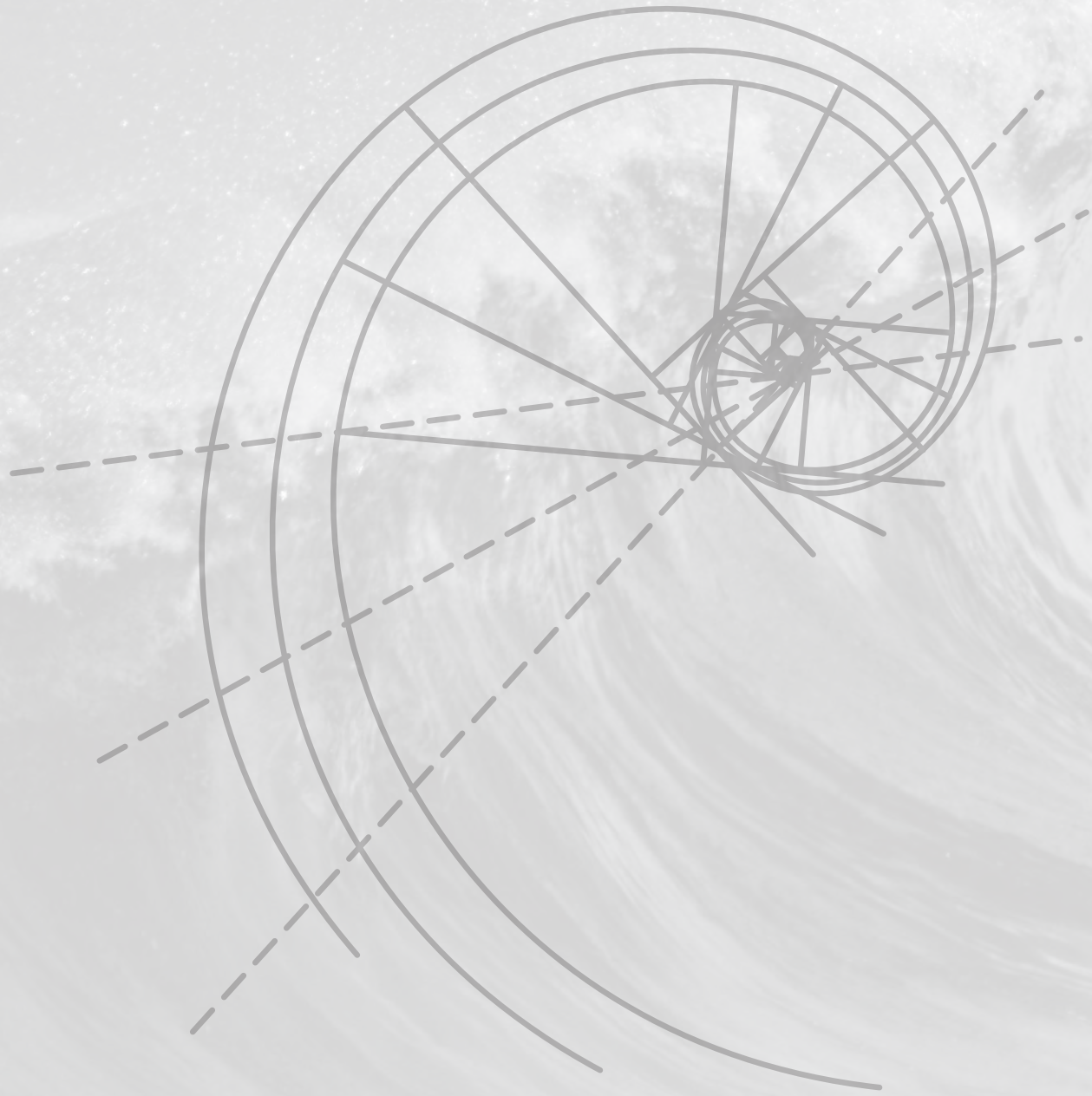

Chapter

3

Intestinal transit time in children with intestinal neuronal malformations mimicking Hirschsprung's disease

B. M. Ure[1], A. M. Holschneider[1], Daisy Schulten[1], W. Meier-Ruge[2]

[1]Department of Pediatric Surgery, The Children's Hospital of Cologne, Germany
[2]Department of Pathology, University of Basle, Switzerland

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Abstract

A total of 106 consecutive children with intestinal neuronal malformations were included in a prospective study. The intestinal transit time was assessed using a modification of Hinton's method. The results of transit time studies, the associated specific histochemical findings, therapeutic procedures, and the clinical course on follow-up assessments over a mean period of 2.4 years were analyzed. The intestinal transit time was prolonged in all 53 patients with aganglionosis and in 37 (69.8 %) out of 53 children with other intestinal malformations. Eight out of 16 children with IND type B had an abnormal transit time, 1 underwent anterior resection, and 2 had a temporary colostomy. In 7 out of 8 children with hypoganglionosis and 9 out of 10 children with a reduced parasympathetic tone the transit time was prolonged. A resection was performed in 7 and 2 of these children respectively. Both patients with heterotopia of the myenteric plexus had a prolonged bowel transit and parts of the large bowel had to be resected. Only 11 out of 17 children with heterotopia of the submucous plexus, dysganglionosis, or immature ganglia had a prolonged transit time, 2 underwent sphincteromyotomy. At follow-up, all patients with malformations other than aganglionosis stated that symptoms had improved and they were willing to tolerate their complaints. However, 25 reported on persistent constipation, 6 on overflow encopresis.

All children who required surgery had a prolonged intestinal transit time, but also 21 (56.8 %) of 37 children who were successfully treated without surgery. None of the 16 children with normal transit had to be operated. It is concluded that specific histochemical findings do not always correlate with delayed intestinal transport. The determination of the intestinal transit time represents an important tool to identify the clinical relevance of histochemical findings in the individual patient.

Introduction

In recent years, numerous intestinal neuronal malformations have been well differentiated from classical aganglionosis (2, 7, 11, 15, 16, 19), but the clinical relevance of these findings is still a matter of discussion (5, 7, 21). Orally applicated radioopaque pellets have been useful in obtaining data on colonic transit abnormalities (3, 9, 10, 13, 18, 21), and in determining the severity of constipation in the individual patient. Therefore, the aim of the present study was to investigate the correlation between specific histopathological findings, the intestinal transit time, and the clinical course in a consecutive series of children.

Patients and methods

From 1989-1995 all patients with intestinal neuronal malformations who were treated in the Department of Pediatric Surgery of the Hospital for Sick Children in Cologne were included in a prospective study (22). Out of 141 consecutive children, 106 (75.2 %) underwent transit time studies and were analysed in detail. In 34 children with ileus or enterocolitis, transit time studies could not be performed due to an immediate surgical treatment. One child was excluded from the study after aspiration of a pellet which was subsequently removed by bronchoscopy. The mean age of the patients included to the study was 4.9 years (SD 5.6), 31 patients were female (29.2%), and 75 were male (70.1 %).

The transit time was determined by a modification of Hinton's method (6). The children ingested 20 radioopaque markers and an abdominal x-ray was taken after 12, 34 and 48 hours. After 12 hours, the pellets should have passed to the ascending colon, after 34 hours, 50 % of the pellets should be evacuated. By 48 hours, 80 % of the markers should have passed.

Suction biopsies were performed according to Noblett (17), and specimens were processed as suggested by Meier-Ruge et al. (13). All specimens were investigated by the Institute of Pathology of the University of Basle/Switzerland. The histochemical methods have been published by Meier-Ruge et al. (12, 13). Parasympathetic fibers were identified by acetylcholinesterase (AChE) staining. Nerve cells of the submucous plexus were visualized by a lactic dehydrogenase (LDH) reaction and the succinic dehydrogenase (SDH) reaction allowed mature cells to be distinguished from immature cells.

For the classification of malformations such as aganglionosis, intestinal neuronal dysplasia (IND) type A and B, and hypoganglionosis, the result of a consensus conference held in 1990 (2) was used. Not classifiable dysganglionoses such as heterotopic nerve cells of the submucous or myenteric plexus, a reduced parasympathetic tone, mild dysganglionosis and immature ganglia or hypogenetic nerve cells were defined according to Meier-Ruge et al. (11,12,13).

Follow-up was performed in all patients included in the study over a period of 2.4 years (mean, SD 1.4). Children and/or parents were interviewed before treatment and during follow-up on specific symptoms such as constipation, overflow encopresis, or diarrhoea. Constipation was defined by stool retention for at least 5 days (21). Conservative treatment and operative procedures such as anterior resection according to Rehbein, transient enterostomy, and sphincteromyotomy were recorded.

Results

Out of 106 children 53 (50 %) had classical aganglionosis and another 53 various intestinal malformations (Table 1). No patient had normal histochemical findings.

The intestinal transit time was prolonged in all patients with aganglionosis and in 37 children (69.8 %) with other intestinal malformations. Eight out of 16 children with IND type B had an abnormal transit time (Table 1) and 1 (6.2 %) underwent anterior resection due to untreatable constipation (Fig. 1). Two of these children with IND type B had a temporary colostomy which was closed without further resection and subsequent medical treatment. In 7 out of 8 children with hypoganglionosis and 9 out of 10 children with a reduced parasympathetic tone the transit time was prolonged. A resection was performed in 7 and 2 of these children respectively. Both patients with heterotopia of the myenteric plexus had a prolonged transit time and parts of the large bowel had to be resected. Out of 13 children with heterotopia of the submucous plexus or dysganglionosis 9 had prolonged transit, 2 of these underwent sphincteromyotomy. Two out of 4 children with immature ganglia had prolonged transit, none was operated.

All children who underwent operative therapy had a prolonged transit time (Fig. 2), but also 21 (56.8 %) of 37 children who were successfully treated without surgery. None of the 16 children with normal bowel transit had to be operated.

Within the follow-up period, 1 patient with hypoganglionosis died from reasons not related to the intestinal malformation. At follow-up, 33 (63.5 %) out of 52 children without aganglionosis reported to suffer from symptoms, 25 had constipation, 6 overflow encopresis, and 2 occasional attacks of diarrhoea. All persistent symptoms were managed medically at the time of the last follow-up assessment. All patients stated that their symptoms had improved and they were willing to tolerate their complaints.

Discussion

The assessment of the intestinal transit time seems to offer an opportunity to determine the clinical impact of intestinal neuronal malformations. Numerous methods have been introduced and until today, no single technique is generally accepted. Metcalf et al. (14) applied 3 different forms of markers on 3 consecutive days. The authors performed an abdominal x-ray on day 4, Papadopoulou et al. (18) on day 5. Schindlbeck et al. (20) gave 20 markers on 6 consecutive days and took an x-ray on day 7. Meier et al. (10) applied 10 markers on 6 consecutive days and also performed an abdominal x-ray on day 7. It has to be noted that most of these methods were established in adult series with small numbers of individuals investigated for establishing normal values of transit time.

There are specific problems in assessing the intestinal transit time in children. In particular in young children, the application of markers often is difficult. In addition, it has been postulated that the transit time in children compared to adults is somewhat shorter (1), but reliable data derived from large series are not available. Metcalf et al. (14) reported on a mean total colonic transit time of 36 hours in 49 healthy adults, Chaussade et al. (4) on a mean transit time of 34 hours in 22 individuals. Bautista Casanovas et al. (3) determined a similar mean transit time of 38 hours in 10 healthy children. Therefore, in this study a modification of Hinton's method (6) was used. The total time of assessment was reduced to 48 hours and 20 markers were given on only one occasion. It was decided to perform an x-ray examination after 12, 34 and 48 hours to distinguish the transit time of the small bowel from the colon, and to identify an occasional colonic retroperistalsis.

The transit time was prolonged in all children with classic aganglionosis and in 70 % of the children with other histochemical findings. Only half of the children with IND type B had an abnormal transit time. Surgical

therapy including 1 resection was necessary in 3 of these children. In other series, varying degrees of severity of IND type B have been reported. Koletzko et al. (9) found no significant difference in transit time in 11 patients with abortive IND, 4 with classic IND, and 15 patients with normal histology. Munakata et al. (15) found severe constipation requiring resection in 5 out of 9 patients with IND type B. Three of these patients died. It is concluded, that only some patients with histochemical signs of IND type B have a relevant impairment of bowel transport. The determination of the transit time using radioopaque markers may help to identify the clinical relevance of the disease in the individual patient.

Hypoganglionosis and heterotopia of the myenteric plexus are known to cause severe symptoms (16, 21). All except 1 patient of the present series with these findings had a prolonged transit time and were resected. Munakata et al. (16) reported on a similar severity of hypoganglionosis in 12 children of whom 11 underwent a pull-through operation.

Meier-Ruge (11) stated that heterotopia of the submucous plexus is extremely common and seems to be a normal variant. However, in this study 9 out of 13 children with heterotopia of the submucous plexus had a prolonged transit time, 2 required sphincteromyotomy.

Children with a reduced parasympathetic tone in the rectal mucosal biopsy may have another underlying anomaly of the myenteric plexus (22), but full-thickness biopsies would be necessary to establish the diagnosis. An abnormal transit time was found in 9 out of 10 children with a reduced parasympathetic tone. These findings need further investigations.

There is no universally accepted technique for the investigation of intestinal neuronal malformations. In this study, the enzymehistochemical methods such as AChE-, LDH-, and SDH-reaction were used as suggested by Meier-Ruge et al. (11, 12), Schärli (19), and Holschneider et al. (7). The incidence of malformations obtained using these methods was similar to a previous series of children investigated by Meier-Ruge (11). However, the results of the present analysis do not indicate a clinical relevance for all of these specific findings. In approximately half of the patients with IND type B, heterotopia of the submucous plexus, dysganglionosis or immaturity of nerve cells, the bowel transport of markers was unimpaired. This correlates with a report of Kobayashi et al. (8), who identified some enzymehistochemical findings in normal individuals. An increase in AChE activity was seen in 4 out of 23 specimens of normal colon, giant ganglia were seen in 2 neonates, hyperganglionosis in 3, and ectopic ganglion cells in another 2.

All children of the present study who required surgery had a prolonged intestinal transit time. No child with normal transit required operation. Therefore, the determination of the intestinal transit time using radio-opaque markers represents an important tool to identify the clinical relevance of specific histochemical findings in the individual patient.

Table 1 Histochemical diagnosis and transit time in 106 children with intestinal neuronal malformations included to the study from 1989-1995.

Histochemical diagnosis	n	Prolonged transit time n
Aganglionosis	53	53
IND* type B	16	8
Hypoganglionosis	8	7
Heterotopia of the myenteric plexus	2	2
Heterotopia of the submucous plexus/ mild dysganglionosis	13	9
Reduced parasympathetic tone	10	9
Immaturity	4	2

*IND; intestinal neuronal dysplasia

Fig.1 Frequency of conservative treatment, anterior resection, temporary colostomy, or sphincteromyotomy in 53 children with intestinal neuronal malformations mimicking Hirschsprung's disease: IND Type B = intestinal neuronal dysplasia (IND) type B (n = 16); hypoganglionosis (n = 8), heterotopia of the myenteric plexus (n = 2); heterotopia of the submucous plexus/mild dysganglionosis (n = 13); reduced parasympathetic tone (n = 10); immaturity (n = 4).

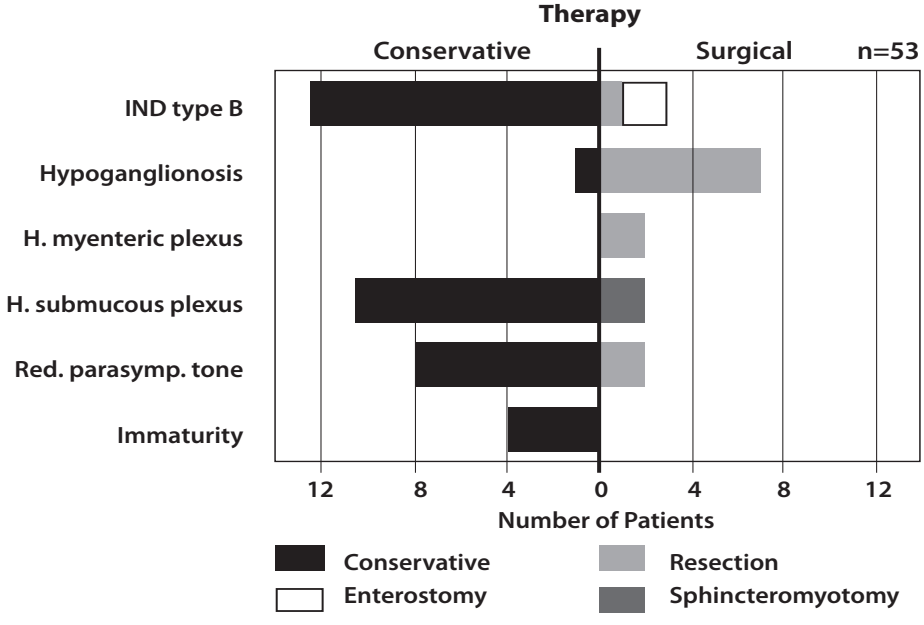
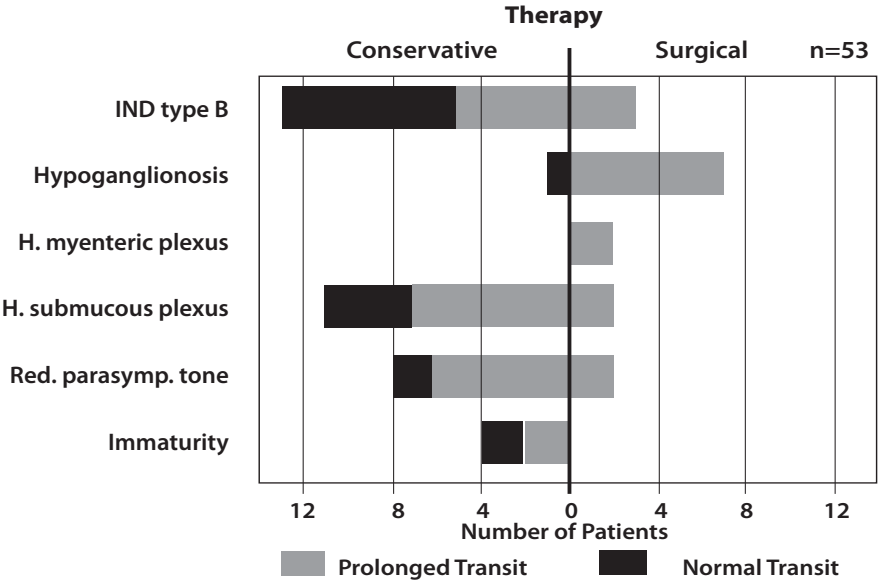


Fig. 2 Transit time according to conservative or surgical treatment in 53 children with intestinal neuronal malformations mimicking Hirschsprung's disease: IND Type B= intestinal neuronal dysplasia (IND) type B (n = 16); hypoganglionosis (n = 8), heterotopia of the myenteric plexus (n = 2); heterotopia of the submucous plexus / mild dysganglionosis (n = 13); reduced parasympathetic tone (n = 10); immaturity (n = 4).



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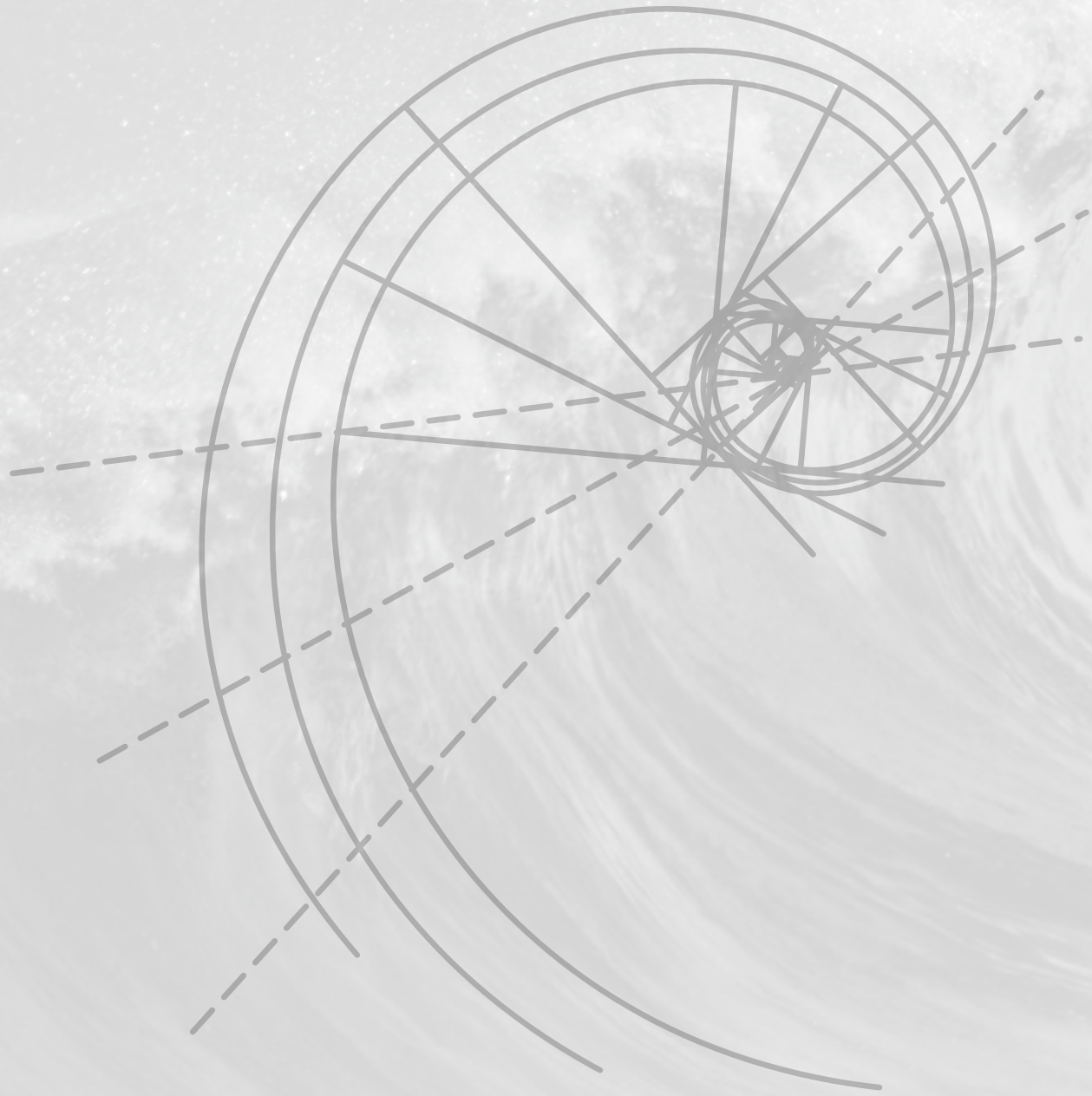

Chapter

4

Proximal segment histology of resected bowel in Hirschsprung's disease predicts postoperative bowel function

D. Schulten[1], A. M. Holschneider[1], W. Meier-Ruge[2]

[1]Department of Pediatric Surgery, The Children's Hospital, Cologne, Germany
[2]Department of Pathology, University of Basle, Switzerland

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Abstract

The authors present an overview of 101 patients operated for Hirschsprung's disease by Rehbein procedure. Special attention is directed to the histomorphological findings in the proximal segment of the resected bowel specimens. A strong link was confirmed between these specific features and postoperative bowel function. A histologically regular proximal bowel segment generally predicted good postoperative bowel function with a constipation rate of 10.5%. In patients with intestinal neuronal dysplasia (IND) of the proximal segment the overall c1inical result remained unchanged, although the constipation rate rose to 17.8%. Postoperative bowel function was seriously affected in cases characterized by proximal segment hypoganglionosis with a constipation rate of 23.1% and an additional 7.7% with encopresis. Finally, the distinct group of children with aganglionosis of the proximal segment followed a complicated postoperative course with secondary bowel resections and recurrent episodes of enterocolitis. In addition, the authors state their general observation that histological findings become less important whenever a more extensive resection than left hemicolectomy is required. Discussing the results, guidelines are given to further patient treatment once the particular proximal segment histology is diagnosed.

Introduction

Primary surgery for Hirschsprung's disease and allied disorders commonly leads to satisfactory bowel function. A small group of children, however, will still experience constipation or other bowel dysfunction. These include encopresis and remittent episodes of intestinal obstruction or, conversely, diarrhea or even enterocolitis.

Purpose and Definition

In order to assess postoperative outcome we looked for a correlation of histological findings in the resected bowel segments with the c1inical results. We observed the importance of histological features nearest to the proximal resection site. We called this site *the proximal segment.*

Materials and Methods

Our series consisted of 101 children who underwent primary surgery between 1979 and 1997 at our institution. Their age at the time of operation ranged from 2 months to 13.1 years, an average of 1.9 years. 74 patients were male, that is, a male/female ratio of 2.7/1. All underwent complete preoperative evaluation including suction biopsy, determination of intestinal transit time, x-ray examination, electromanometry and were indicated for surgery. All were submitted to the Rehbein procedure.
The proximal segment of each surgical specimen was prepared transversally to the length of the gut. Native tissue was cut in a cryostat at a temperature of - 20°C in sections of 15 µm thickness, which is equivalent to a paraffin section of 4 - 5 µm thickness, due to 70% volume loss by spreading and drying of native sections on microscopic slides.
The dyeing techniques (8) used were: acetylcholinesterase (AChE) to visualize fibers of parasympathetic origin, lactic dehydrogenase (LDH) to stain the plexus submucosus and thereby differentiate small nerve cells from Schwann cells. Succinate dehydrogenase (SDH) was used to determine cell maturity. A complete examination of all specimens was carried out.
In our study we directed special attention to histomorphological findings in *the proximal segment.* After consideration of all relevant criteria,

the histological nature of the proximal segment was characterized and the specimens grouped as follows: regular histological patterns, intestinal neuronal dysplasia of submucous plexus, hypoganglionosis, aganglionosis, dysganglionosis, immaturity and heterotopy of myenteric plexus.
All children were seen postoperatively at regular intervals ranging from 0.85 to 14.4 years (average 4.5 years). Their present symptoms were recorded and the state of bowel function assessed. A correlation was established between proximal segment histology and postoperative bowel function.

Results

Histological characterization of the proximal segment revealed regular histological patterns in 38 cases (37.6%). Intestinal neuronal dysplasia of the proximal segment was diagnosed in 28 cases (27.7%), hypoganglionosis in 26 cases (25.7%). The severe histological picture of persistent aganglionosis of the proximal segment was found in 4 cases (4.0%). Dysganglionosis of myenteric plexus was diagnosed in 3 cases (3.0%). Finally, there was one case of nerve cell immaturity and one case of heterotopy of the myenteric plexus (Fig. 1). Correlating these groups of *proximal segment histology* to their c1inical effect we observed the following aspects: A histologically *regular* proximal bowel segment generally predicted good postoperative bowel function by a figure of 76.3%. Of the remainder, 10.5% suffered from persistent constipation, while 5.3% had enterocolitis and 2.6% episodes of diarrhea in cases where extensive colon resection had to be performed. Included were two deaths: the first occurred during cardiac surgery for atrioventricular defect and the second was due to sepsis bearing multiple malformations with microcephaly (Fig. 2). Neuromorphological alterations of the submucosal plexus such as in *IND* were of less importance if myenteric plexus was regular, as these children showed a similar postoperative pattern: 78.6% had normal bowel movements, while we observed a slight increase in constipation rate to 17.8%. One case complained of incontinence probably due to sphincter impairment after internal sphincter myectomy (Fig. 3). When the proximal segment was characterized by hypoganglionosis, we observed an increase in constipation rate to 23.1% and overflow encopresis in 7.7%. Episodes of

diarrhea occurred in 15.4% (Fig.4). In the distinct group of aganglionosis in the proximal segment, the frozen sections performed at surgery suggested the presence of ganglion cells although postoperative stains could not definitely identify these. All four patients experienced serious postoperative problems. In two of them, we had to perform a second colon resection: in the first case extending a rectosigmoidectomy into a left colectomy, and in the second case extending a transversectomy into an ascendectomy. Both of them are now doing well. Of the other two in this group, one child with total colonic aganglionosis suffered from recurrent episodes of enterocolitis even after total colectomy had been performed. In this case, aganglionosis extended into the terminal ileum. The last child died of aganglionosis of the whole gastrointestinal tract (Fig. 5). Immaturity and dysganglionsis of the myenteric plexus had no adverse effect on the outcome as the four children belonging to these groups had normal bowel movements. The only child diagnosed with heterotopy of the myenteric plexus is presently without symptoms.
A general observation of our study was that histological findings in the proximal segment became less important whenever an extensive colon resection was indicated. Of those who required a transversorectostomy or an even more extensive colon resection, 72.1% were observed to have regular bowel function although only one third of them (32.3%) had normal proximal segment histology.
Excluding these cases of extensive colon resection from the series would not significantly change the above-mentioned correlations of proximal segment histology to c1inical outcome in the various subgroups (Fig. 6).

Discussion

Histopathological evaluation of the proximal segment in resections for Hirschsprung's disease and allied disorders is of major importance for the pediatric surgeon because of the strong link between proximal segment histology and postoperative outcome.
Whereas the histopathological diagnosis of Hirschsprung's disease is well established by the typical picture found in rectal biopsies [3,11,12], diagnosis of anomalies of the myenteric plexus allow indirect conclusions only [9,10,13]. The specific histopathological classification of the proximal segment of a resected specimen and its significance in predicting postoperative function have recently attracted particular interest.

In 1995, Kobayashi et al. [7] described the presence of IND at the proximal margin of resected bowel specimens in pull-through operations for Hirschsprung's disease. In their series, 10 out of 31 patients demonstrated this association. All of these 10 suffered from postoperative constipation. As opposed to this, Hanimann et al. [2] observed no significant difference regarding postoperative outcome after pull-through operations for Hirschsprung's disease in 11 cases with associated IND compared to 36 cases without this association. As the incidence of Hirschsprung-associated IND in our study was similar to both studies cited above, we could neither confirm nor negate a complete correlation to postoperative constipation in our subgroup of IND in the proximal segment; we observed a slight increase in constipation rate in the IND group compared to those with a regular proximal segment.

In the above mentioned Kobayashi study, serious postoperative problems were observed in one child with aganglionosis and in another one with hypoganglionosis of the proximal segment. We could confirm this important observation and further specify the correlation to postoperative outcome in our 4 children with aganglionosis and in 26 cases of hypoganglionosis.

In both subgroups direct consequences may result as it unvariably means that misfunctioning colon sections are still left in the abdomen. This is the reason why a great number of children with hypoganglionosis in the proximal segment present again with severe constipation after primary surgery. Therefore, follow-up in this group is essential. It should be carried out specifically and at short intervals in order to prevent obstruction and fecaloma. Parents should be kept c1early informed about the type of illness and the typical complications.

With respect to the group of children diagnosed with aganglionosis in the proximal segment, their postoperative course is even more difficult. Although the number of these children in this group was small, we were able to show that none of them developed regularly in the postoperative period. Indeed, they either required a second colon resection or presented with enterocolitis. In these cases, additional colonic wall biopsies taken from the preternatural anus are indispensible to determine further surgical strategy.

Recent investigations by Kobayashi, Puri et al. [4 - 6] and Dudarkinová et al. [1] dealing with a variety of histochemical reactions have proven to be useful for intraoperative histochemical examination of resected bowel margins. A consensus should be reached on a standardized method for

such intraoperative evaluations. Based on standardized criteria, the precise extent of pathological bowel would determine resection site and consequently further improve postoperative results in the future.

Fig. 1 Distribution of histological characters in the proximal segment of all 101 specimens.

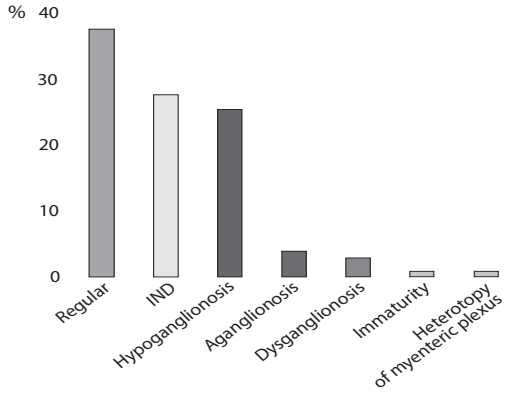


Fig. 2 Correlation of regular histology in the proximal segment to clinical effect.

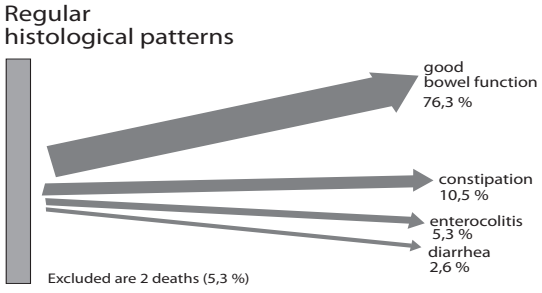


Fig. 3 Correlation of IND in the proximal segment to clinical effect.

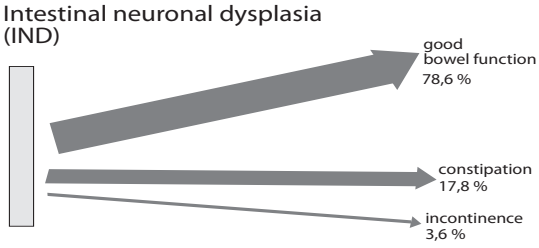


Fig. 4 Correlation of hypoganglionosis in the proximal segment to clinical effect.

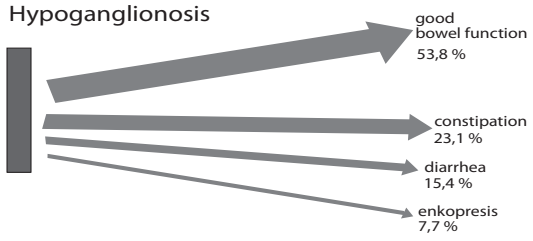


Fig. 5 Correlation of aganglionosis in the proximal segment to clinical effect.

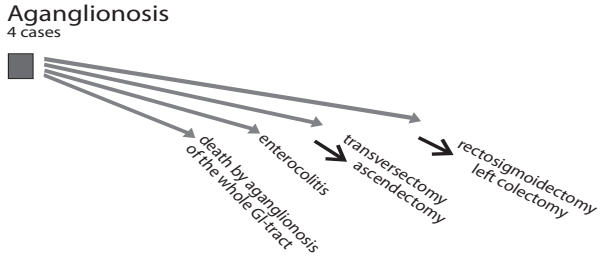
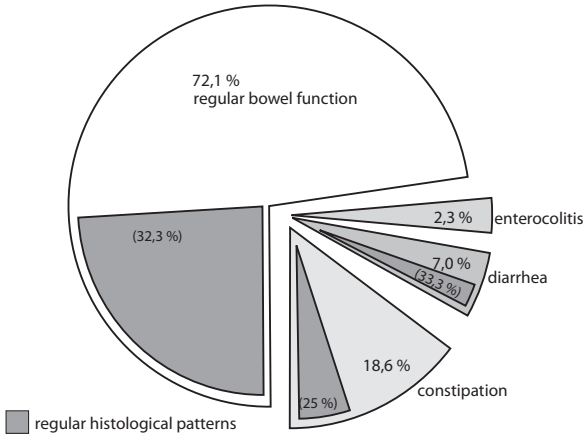


Fig. 6 Correlation to clinical effect in the subgroup of extensive colon resection (43 of 101 cases).



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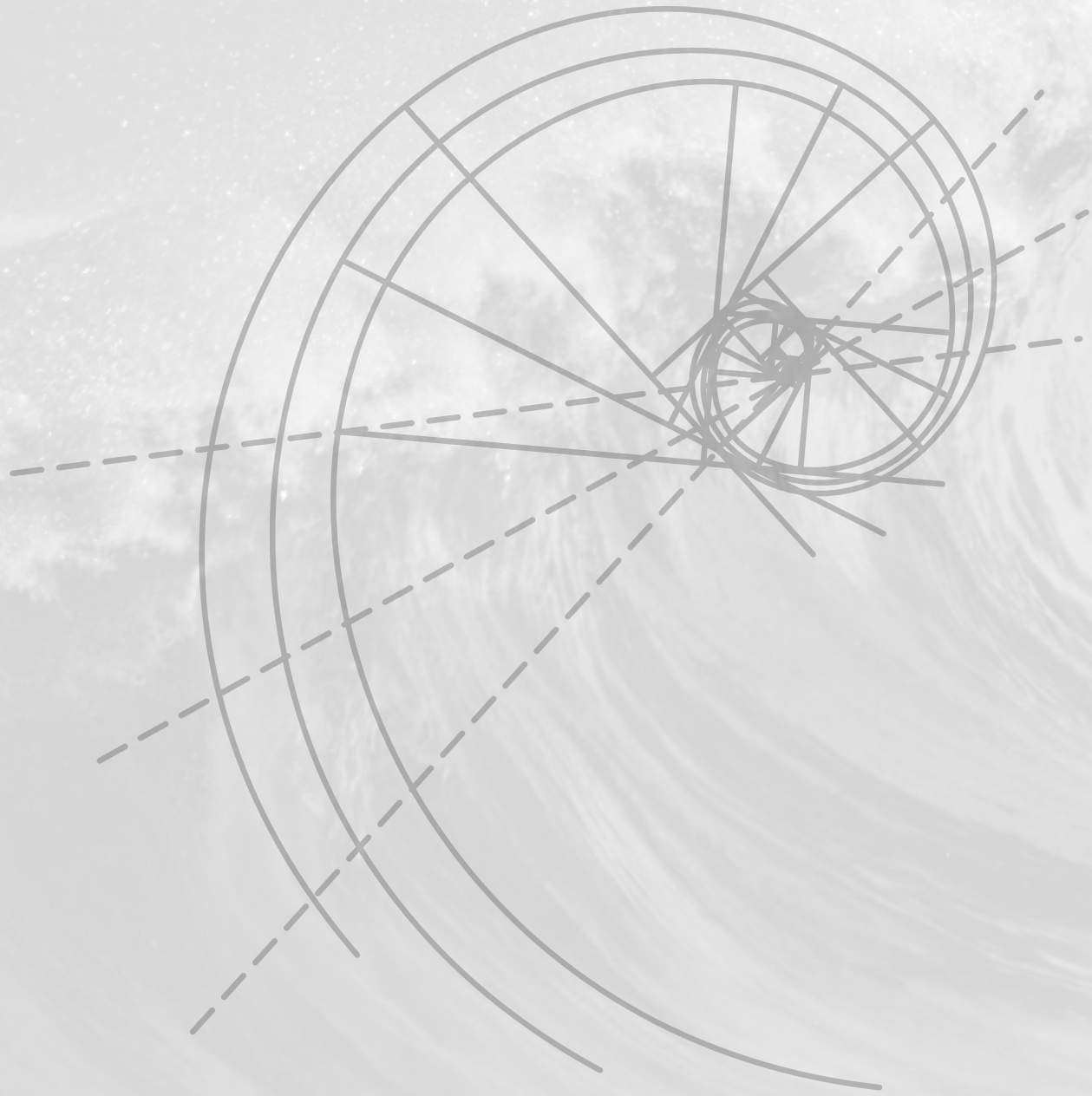

Chapter

5

Duhamel procedure: a comparative retrospective study between an open and a laparoscopic technique

D. Vieira Travassos[1], N. M. A. Bax[1,2], D. C. Van der Zee[1]

[1]Department of Pediatric Surgery, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands
[2]Department of Pediatric Surgery, Sophia Children's Hospital, Erasmus Medical Centre, Rotterdam, The Netherlands

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Abstract

Background: Few studies are available comparing open with laparoscopic treatment of Hirschsprung's disease. This study compares a laparoscopic series of 30 patients with a historical open series of 25 patients.

Methods: The charts of all patients having had a Duhamel procedure in the period from June 1987 through July 2003 were retrospectively reviewed. Open procedures were performed until March 1994. Patients with extended aganglionosis, pre-Duhamel ostomy, or syndrome were excluded from the study. End points were intraoperative complications, postoperative complications, time to first feeding, hospital stay, and outcome at follow-up such as stenosis, enterocolitis, constipation, fecal incontinence, and enuresis.

Results: Twenty-five patients had an open Duhamel (OD) and 30 had a laparoscopic one (LD). There were no differences in patient characteristics and there were no intraoperative complications in either group. Time to first oral feeds was significantly longer in the OD group as was the duration of hospital stay. No significant differences at follow-up were observed but there was a tendency for a higher enterocolitis rate in the LD group. In contrast, the adhesive obstruction and enuresis rates were higher in the OD group. Cosmetic results were superior in the LD group.

Conclusions: Except for a significantly shorter hospital stay and shorter time to first oral feeds in favor of LD, no significant differences could be observed. The cosmetic result was not an end point but there was no doubt that it was better in the LD group. Although not statistically significant different, there were no adhesive bowel obstructions in the LD group compared with 3 of 25 in the OD group. Fecal incontinence was not encountered in either group.

Introduction

The treatment of Hirschprung's disease has become less invasive over the years. For a long time the surgical treatment was performed in three tempi: the creation of a proximal diverting ostomy, resection of the aganglionic bowel segment, and restoration of bowel continuity. Since the 1990s the operation is usually performed in one session, without ostomy [1–3]. In several centers the operation is now undertaken shortly after birth, eliminating the need for bowel washouts in the period between diagnosis and definitive surgical treatment.

More recently minimal access techniques have been introduced for taking biopsies to determine the proximal extension of the disease and for dissection of the aganglionic part of the bowel to be removed [4–6]. Transanal resection of the aganglionic colon has also been performed without taking biopsies at the beginning of the operation in cases with presumed classic extension of the disease [7].

The treatment for Hirschsprung's disease in our institution has been the Duhamel technique for a long time. With the introduction of minimal access techniques in the early 1990s, we developed a laparoscopic variant of the open technique and published preliminary results in 1995 [4]. There is little doubt that the laparoscopic variant of the open Duhamel leads to less pain, a quicker recovery, and better cosmesis, but the question arises whether the operation is as safe as the open one and whether the functional results are comparable. In this study we compare a series of laparoscopic Duhamel procedures with a historical series of open Duhamel procedures.

Materials and methods

The charts of all patients who underwent a Duhamel procedure in the period from June 1987 through July 2003 were retrospectively analyzed. From June 1987 through March 1994 the Duhamel procedure was performed in an open way (OD), and from March 1994 through July 2003 it was performed laparoscopically (LD).

To obtain a relatively homogeneous group of patients, patients were excluded from the study for the following reasons: preoperative colostomy, extended aganglionosis, trisomy 21, Waardenburg syndrome, or other associated malformations.

Preoperative bowel preparation consisted of antegrade washout until the effluent became clear [8].

The laparoscopic technique was described earlier [4]. In short, the extension of the aganglionosis was diagnosed by frozen section examination of seromuscular biopsies taken during surgery. Originally the dissection of the rectum was performed circumferentially up to the pelvic floor, allowing the rectal stump to be closed transanally. The latter was difficult and required considerable traction on the stapled side-to-side anastomosis in order to reach the upper part of the stump [4]. The technique was therefore modified. The anterior dissection was limited to just below the peritoneal reflexion, while posterior dissection was done up to the pelvic floor. Dissection of the bowel in the proximal direction was close to the bowel wall up to a good location for a biopsy. Either the rectum was amputated at the level of the peritoneal reflexion after placing a proximal ligature around the rectum to prevent leakage or the mobilized colon was everted through the anus. The everted rectum was then transected under traction close to the anus, while the bowel was further exteriorized up to the good biopsy location. The everted bowel was then amputated and closed. The everted bowel was reintroduced into the abdomen as was the remaining rectum.

About 0.5 cm above the dentate line a transverse incision was made in the posterior rectal wall and the retrorectal space was entered to meet the space dissected from above. The proximal end of the bowel was grasped, pulled through, and anastomosed circumferentially with the created opening in the posterior rectum. A side-to-side anastomosis was then made between the anterior aganglionic rectum and the posterior pulled-through ganglionic bowel using an EndoGIA (blue cartridge 3.5cm long; Tyco Heathcare) under laparoscopic control. Usually two cartridges needed to be fired. Finally, the upper rectum was closed laparoscopically with a running 2 x 0 Vicryl suture. Outcome measures included postoperative complications, hospital stay, and long-term outcome such as constipation, enterocolitis, fecal incontinence, enuresis, stenosis, and adhesive obstruction.

The data were statistically analyzed by using SPSS v9.0 (SPSS Inc., Chicago, IL). A p value of less than 0.05 was considered significant. For comparing weight and age between the two groups the t test was used, whereas for hospital stay and start of oral feeding the Mann-Whitney U test was used. Fisher's exact test was used for comparing the postoperative complications and additional surgical procedures. Data are given as mean (range) unless stated otherwise.

Results

In total 117 patients were operated on during the study period. Sixty-two patients underwent an open Duhamel in the period from June 1987 through March 1994, and 55 had a laparoscopic Duhamel in the period from March 1994 through July 2003. After applying the exclusion criteria 25 patients (21 males and 4 females) who underwent an open Duhamel remained and 30 patients (23 males and 7 females) who had a laparoscopic Duhamel remained. Patient characteristics are shown in Table 1. There were no statistically significant differences between the groups with respect to gender or age at the time of operation.

No intraoperative complications were recorded in both groups. The operative time for the open group could not be traced anymore. In the LD group the mean operative time was 4.8 h (range = 2.3–9 h).

Postoperative events are given in Table 2. Two patients in the LD group underwent a second operation in the early postoperative period: One because of leakage of the rectal stump, which was treated by laparotomy and ileostomy, and the second had laparoscopy because of suspicion of leakage that could not be confirmed. There was a statistically significant difference between the groups with respect to length of hospital stay ($p < 0.001$) and time of first oral intake ($p < 0.001$).

Because of the study design the period of follow-up is different between the two groups. Two patients in the LD group were readmitted for dilatation of the anorectum for stenosis. In one of these patients a rectal spur needed to be transected; this was performed under laparoscopic control. In this patient initially only one cartridge had been used. Reoperation was carried out in one OD patient and in two LD patients.

Although statistically not significant, there was a higher incidence of admission for enterocolitis in the LD group. There were more children with adhesive obstruction and with enuresis in the OD group, but again the differences was not statistically significant (Table 3).

Discussion

Hirschsprung's disease is basically incurable. Even when the proximal transection plane of the bowel shows a normal plexus at pathologic examination, there is no guarantee of a good outcome because the distal rectum is and remains abnormal. The best that surgery can achieve is a delicate balance between constipation and incontinence. More often

than not the balance tips in one direction. End points are difficult to set and final results are therefore difficult to evaluate.
Hirschsprung's disease is a relatively rare disease and is heterogeneous in the sense that its extension varies and that it may be part of a syndrome. To obtain a group of patients that was as homogeneous as possible, many variables in the present study were excluded. The disadvantage of that is that the subgroups become smaller which makes it harder to obtain significant differences between the groups. With these limitations in mind, we can conclude that there was no difference in intraoperative complication rate. Although the operative times for patients in the OD group were not available, the operative times for patients in the LD group were long, which emphasizes that the laparoscopic procedure is not simple. The difference in starting time of oral feeding and in postoperative hospital stay were significantly longer in the OD group. The first seems to be the result of bias as the postoperative feeding protocol changed over the years toward faster introduction of feeding. The same may apply to the shorter postoperative hospital stay in the LD group although this is less obvious. There were no significant differences in postoperative complications or in the follow-up end points. However, relatively more patients in the LD group were readmitted for enterocolitis, maybe more rectum is left behind with LD. Better functional results have been reported when a short rectal pouch is left [8]. Although not statistically different, adhesive bowel obstruction was seen in the OD group only and the same applies for enuresis. The cosmetic results were definitely better in the LD group.

Conclusion

The laparoscopic variant of the Duhamel procedure is not simple, as reflected by its long operation time. There seems to be no essential difference between the open and the laparoscopic procedure with respect to postoperative complications or functional results at follow-up. Although there is a tendency for a higher enterocolitis rate in the LD group, lower adhesive obstruction and enuresis rates were encountered. There is no doubt that the LD is cosmetically superior. Despite the fact that the transanal approach is becoming more popular in recent years, there certainly remains a place for the laparoscopic Duhamel–Martin procedure, particularly when extended Hirschsprung's disease is present.

Table 1. Patient characteristics

	Open Duhamel	Laparoscopic Duhamel
Gender (m,f)	21, 4	23, 7
Age at diagnosis (months)	4.2 (0.13–72.4)	4.6 (0.7–67.8)
Age at operation (months)	6.8 (1.2–74.9)	8 (0.9–72)
Weight at operation (kg)	7.1 (4.5–18.5)	8 (3.2–22)
Operation time (h)	not available	4.5 (2.3–9)

Data given as median (range)

Table 2. Postoperative events

	Open Duhamel (n = 25)	Laparoscopic Duhamel (n = 30)
Postoperative fever	3	1
Leakage of rectum stump	0	1
Abscesses	0	0
Start of oral feeding (days)	5.1 (4–8)	3.4 (2–9)
Hospital stay (days)	7.8 (6–13)	6 (3–15)

Table 3. Results at follow-up

	Open Duhamel (n = 25)	Laparoscopic Duhamel (n = 30)
Follow-up (months)	87.8 (7–211)	39.5 (–113)
Reoperation (Duhamel)	1	2
Stenosis	0	2
Obstructive ileus	3	0
Admission for enterocolitis	3	9
Admission for constipation	7	5
Incontinence	0	0
Enuresis	3	0

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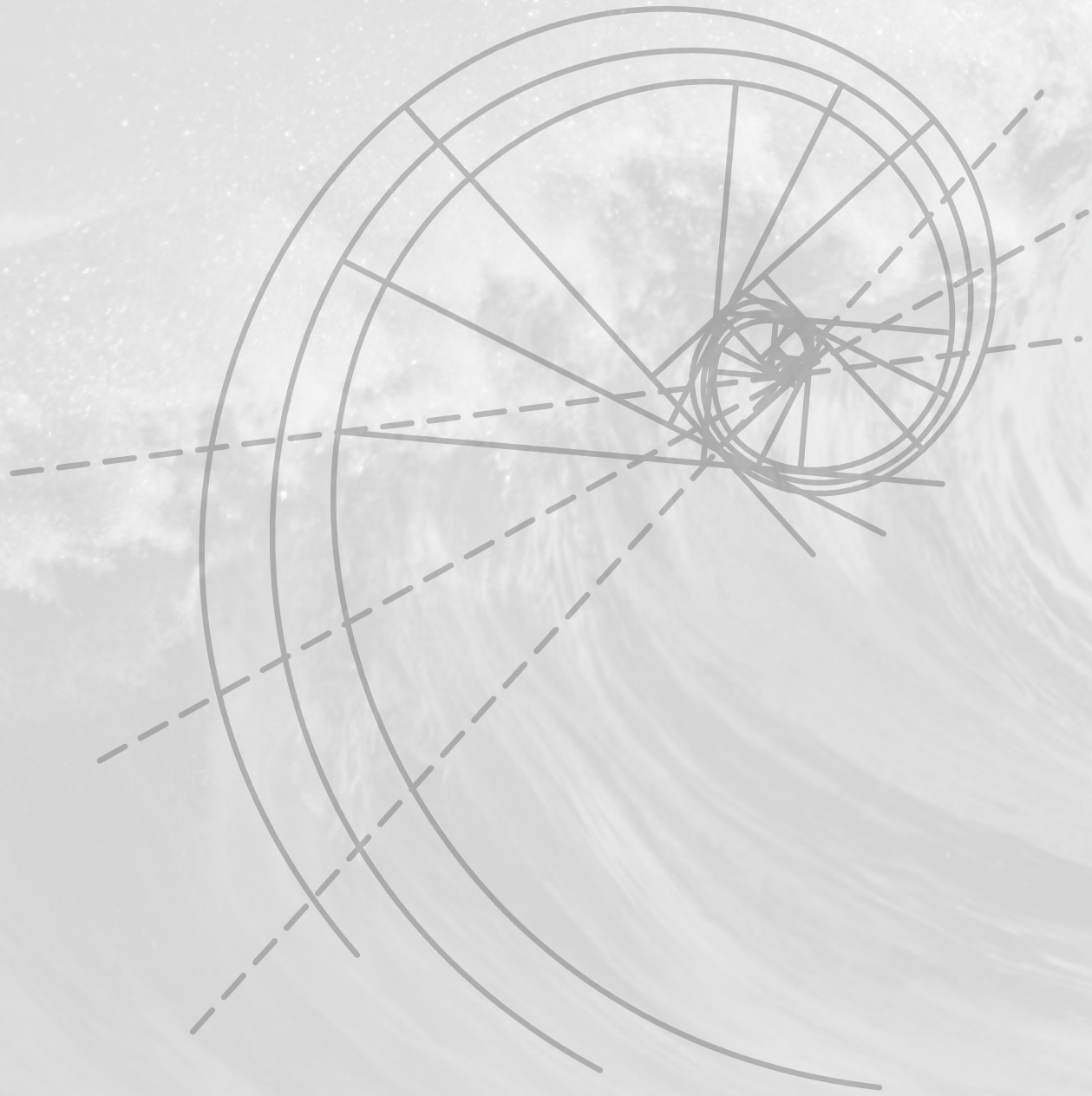

Chapter

6

Hirschsprung's disease in children with Down syndrome: a comparative study

D. Travassos[1], M. van Herwaarden-Lindeboom[1], D. C. van der Zee[2]

[1]University Medical Centre Utrecht, Pediatric Surgery, Utrecht, Netherlands
[2]Wilhelmina Children' s Hospital, Department of Pediatric Surgery, Utrecht, Netherlands

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Abstract

Background and aim: There is controversy in the literature regarding the outcome after surgical treatment of Hirschsprung's disease in children with Down syndrome (DS). The aim of this study was to compare the outcome of our series of DS children with Hirschsprung's disease to our series of children without Down syndrome (NDS) with Hirschsprung's disease. The impact of laparoscopy within the DS group was analyzed.
Material and methods: Between March 1987 and August 2008, 149 children were operated on for Hirschsprung's disease. 20 children of this group were additionally diagnosed with Down syndrome. All children underwent either an open or a laparoscopic Duhamel procedure. We evaluated postoperative hospital stay, short-term complications and the incidence of enterocolitis, constipation and incontinence.
Results: 20 patients (13.4%) in this series had Down syndrome. There were no significant differences in the extent of aganglionosis between children with or without Down syndrome. There were no intra-operative complications and no conversions. Postoperative leak occurred significantly more often in children with DS (n = 5, 25%) compared to NDS children (n = 1, 0.7%; $p < 0.0001$). Postoperative leakage-related abscess formation was higher in the DS group (n = 3, 15%) compared to the NDS group (0 %). Within the DS group there was no significant difference between open or laparoscopic Duhamel procedure with regard to these postoperative complications. Postoperative hospital stay was significantly longer in the DS group compared to the NDS group ($p < 0.05$). In the DS group there was a slightly shorter postoperative stay after laparoscopic Duhamel procedure. Mean long-term follow-up was 5.1 years. One death occurred in the DS group 9 months postoperatively due to sepsis and cardiomyopathy. Severe constipation was present significantly more often in DS children (n = 11, 55%) compared to NDS children (n = 29, 22.3%; $p < 0.01$). There was no difference in incontinence between DS and NDS children. Enterocolitis occurred more frequently in DS patients after operation (40 [31% NDS] vs. 9 [45% DS]; $p = 0.038$).
Conclusion: compared to NDS children, children with DS have a higher rate of postoperative complications and a longer hospital stay. During long-term follow-up most patients with DS are severely constipated and have a higher incidence of enterocolitis.

Introduction

It is known from the literature that children with Down syndrome (DS) are more vulnerable when it comes to surgery than children without Down syndrome (NDS) [1, 2]. In particular in cases, such as Hirschsprung's disease, where major surgery is warranted, DS children are prone to more complications [2, 3]. DS children also seem to do less well than NDS children with regard to outcome after surgery. However, some publications indicate that the outcomes of DS children do not differ from those of NDS children [4]. The aim of this study was to compare the outcomes in our series of DS children with Hirschsprung's disease to those of our series of NDS children with Hirschsprung's disease. Furthermore, we evaluated the effect of laparoscopic vs. conventional surgery in the DS group with Hirschsprung's disease.

Materials & Methods

Between March 1987 and August 2008, a group of 149 children were operated on for Hirschsprung's disease. 20 children in this group (14 boys) had Down syndrome. The demographics of our research population are shown in Table 1. All children underwent either an open (mostly prior to 1994) or laparoscopic Duhamel procedure. The laparoscopic technique used in this operation has been described previously [5]. The endpoints of the study were postoperative complications such as leak or abscess, postoperative stay, and long-term outcome including the incidence of enterocolitis, constipation and incontinence. The criteria for enterocolitis were whether the patient was hospitalized for episodes of diarrhea, generalized illness, sometimes accompanied by fever, and abdominal distension. Krickenbeck's grade [6], which was originally used to score constipation and continence during follow-up in anorectal malformations, was used to analyze postoperative constipation and continence (Table 2). In order to facilitate comparison, continence was only evaluated after the age of 4 years. Data were collected from the medical records and the follow-up protocol, put together according to the guidelines of the Dutch Society of Pediatric Surgery.

Statistical analysis

Statistical analysis was carried out using SPSS version 15.0, and data were analyzed using the Mann-Whitney Test. Data on the Krickenbeck grade and the extent of aganglionosis were analyzed using the Chi-square test.

Results

The incidence of DS in our series of patients with Hirschsprung's disease was 13.4 %. Of the 20 DS children, 8 had associated cardiac anomalies, one had congenital esophageal stenosis, and one child additionally had duodenal atresia. The extent of aganglionosis is given in Table 1. There were no significant differences in the extent of aganglionosis between the 2 groups. There were no intra-operative complications and no conversions of laparoscopic Duhamel procedures into open procedures.

Postoperative stay

The postoperative stay was significantly shorter in the NDS group compared to the DS group (9.5 days [DS] vs. 7 days [NDS], $p < 0.05$). An analysis of the postoperative hospital stay after a laparoscopic procedure compared to an open Duhamel procedure in the DS group showed a shorter stay (7 days [Lap] vs. 18 days [Open], $p = 0.08$) for patients in the laparoscopic group. In the NDS group the postoperative stay was significantly shorter after a laparoscopic procedure compared to an open Duhamel procedure (6 days [Lap] vs. 8 days [Open], $p < 0.0001$) (Table 3).

Postoperative complications

Anastomotic leak occurred significantly more often in DS children compared to NDS children (25 % DS vs. 0.7 % NDS, $p < 0.0001$) (Table 3). There was no significant difference in the incidence of anastomotic leak in the DS group when we compared the open to the laparoscopic approach ($p < 0.792$). Of the 7 open procedures performed in DS children, 2 experienced subsequent leakage (28.5 %), and both patients were treated with a diverting ileostomy. Of the 13 laparoscopic procedures performed in the DS group, 3 had leakage subsequently (23.0 %), and all 3 patients were also treated with a diverting stoma. In one of these patients the

EndoGIA® device failed. The incidence of postoperative abscesses was also higher in DS children. We found no abscesses among the 129 NDS children, whereas 3 (15%) patients in the DS group developed a postoperative abscess ($p < 0.0001$). In the DS group we found no difference between the laparoscopic and the open group: 1 (14.2%) abscess occurred in the group of 7 open procedures, and there were 2 (15.3%) abscesses in the group of 13 laparoscopic procedures ($p < 0.95$). All abscesses were secondary to postoperative leakage.

Long-term outcome

The duration of mean follow-up was 5.1 years for both groups (range: 0 – 18 years [NDS]; range: 0 – 13 years [DS]). One death occurred in the DS group 9 months postoperatively due to sepsis and cardiomyopathy. Table 4 shows the data on the long-term outcomes after the Duhamel procedure in DS and NDS children.

Constipation

In the DS group there was a significantly higher incidence of severe constipation (grade III 55 % [DS] vs. 22.4 % [NDS], $p < 0.01$) (Fig. 1).

Incontinence

There was no difference between DS and NDS with regard to incontinence (Table 4). A large majority in both groups displayed no signs of incontinence (Fig. 2).

Enterocolitis

We found a significantly higher incidence of postoperative enterocolitis in the DS group compared to the NDS children (45 % [DS] vs. 31 % [NDS], $p = 0.038$). One patient with Down syndrome had such severe recurrent episodes of colitis that a diverting colostomy had to be performed.

Discussion

As Down syndrome does not occur frequently in association with Hirschsprung's disease, our study included a relatively small number (n = 20) of DS patients in the study group, similar to other series published previously [2–4, 7, 8] . A large series (216 patients) was recently published by Ieiri [9] in a nationwide study in Japan.

We found that 13.4 % of our patients with Hirschsprung's disease had Down syndrome. Quinn et al. [2] found a 13 % incidence of trisomy 21 in their series, and Hackam et al. [4] reported a prevalence of 14 %.
The extent of aganglionosis in children with Down syndrome did not differ significantly from that in children without Down syndrome. In the available literature on children with Down syndrome and Hirschsprung's disease we found a higher incidence of long segment aganglionosis (20 – 40 %) compared to our data [1, 2]. Children with Down syndrome are a vulnerable group when it comes to surgery, but there is only limited literature on the incidence of postoperative complications such as anastomotic leak and abscess after Duhamel procedures in all children with Hirschsprung's disease.
Mattioli et al. found an incidence of 1.8% for anastomotic leak after Duhamel procedure in their series [10]. These complications after Duhamel procedures have not been specifically analyzed in children with Down syndrome. In our series we found significantly more patients with leak and abscess in the DS group ($p < 0.0001$).
The high incidence of anastomotic leak and abscess can be explained by the impaired immunological status and healing observed in children with trisomy 21 [11, 12]. However, immunological status was not investigated in this study. There was no difference in the incidence of leak and abscess between the open and the laparoscopic DS group, indicating that laparoscopy did not have a negative impact on postoperative complications.
The hospital stay of DS patients undergoing a Duhamel procedure was significantly longer compared to NDS children, mainly due to the complications that occurred. Within the group of DS patients we found that hospital stay was shorter after a laparoscopic Duhamel procedure but this difference did not reach significance. The results of this study are in line with the results of our former study into laparoscopic vs. open Duhamel surgery [13].
Enterocolitis is one of the most important and serious complications of Hirschsprung's disease. The incidence of enterocolitis in children with Hirschsprung's disease and DS in the literature varies from 39 % to 54 % [1, 3] and is considered to be related to the impaired immunity of DS children [11]. The HAEC score method published by Pastor and colleagues [14] could not be used for the diagnosis of enterocolitis since we did not routinely perform radiological examinations. Moreover, the authors stated in their conclusion that the interpretation of clinical and

radiological findings in the score was often subjective and needed to be individualized, which was not appropriate for a review study.
Puri et al. [1, 2], Caniano et al. [3] and Morabito et al. [8] found a higher incidence of enterocolitis in their series. On the other hand Hackam and colleagues reported that the incidence of postoperative enterocolitis was similar in the DS and the NDS groups after an average of 22 months follow-up [4]. In our series we also found a high incidence of postoperative enterocolitis (45%) in DS patients. We also found that enterocolitis is more frequent in DS patients compared to NDS children.
As regards constipation our results showed that significantly more DS patients were severely constipated compared to the NDS group. This is similar to the available literature [1, 3].
The higher incidence of constipation in DS children is probably related to the mental retardation in this group of children as described by Moore [15]. According to Wallace [16], patients with DS had a higher incidence of constipation and constipation was also higher in adulthood, even in the absence of Hirschsprung's disease. We did not find any major continence problems in children with DS as described by Catto-Smith et al. [7].

In conclusion, compared to NDS children, children with DS had a higher rate of anastomotic leak, a higher incidence of abscess and a longer hospital stay. Laparoscopy did not influence the rate of complications. During long-term follow-up most patients with DS were severely constipated and had a higher incidence of enterocolitis.

Table 1. Demographics of research population.

Duhamel	**NDS**		**DS**	
Number of cases				
	129		20	
Sex	107M 22F		14M 6F	
Median age	6months (0-129)		6months (1-172)	
extension of aganglionosis				
	Extension	No.	Extension	No.
	Classic	89	Classic	17
	Long segment	31	Long segment	2
	Total aganglionosis	9	Total aganglionosis	1

NDS : children without Down syndrome; DS: children with Down syndrome; M:male; F:female

Table 2 International classification (Krickenbeck) for postoperative results

Voluntary bowel movements	**Yes/no**
Feeling of urge, capacity to verbalize, hold the bowel movement	
Soiling	Yes/no
Grade 1	Occasionally (once or twice per week)
Grade 2	Every day, no social problem
Grade 3	Constant, social problem
Constipation	
Grade 1	Manageable by changes in diet
Grade 2	Requires laxative
Grade 3	Resistant to laxatives and diet

Table 3: Short term results after Duhamel in children with and without Down syndrome.

Duhamel	**NDS group (n=129)**	**DS group (n=20)**	**DS group open (n=7)**	**DS group lapar. (n=13)**
leakage	1	5	2	3
abscess	0	3	1	2
postoperative stay (range)	Mean: 7 days (3-173)	Mean: 9.5 days (3-180)	mean: 18 days (7-180)	Mean: 7 days (3-30)

NDS: children without Down syndrome; DS: children with Down syndrome; open: open procedure; lapar.: laparoscopic procedure

Table 4: Long term results after Duhamel in children with and without Down syndrome.

Duhamel	**NDS (n=129)**		**DS (n=20)**		**Down open (n=7)**		**Down lapar. (n=13)**	
enterocolitis	**Episodes**	**No.**	**Episodes**	**No.**	**Episodes**	**No.**	**Episodes**	**No.**
	1-2	12	1	2	1	2	1	6
	1-3	26	1	6				
	9	1						
	11	1	colostomy	1			Colostomy	1
constipation	**Grade**	**No.**	**Grade**	**No.**	**Grade**	**No.**	**Grade**	**No.**
	3	29	3	11	3	3	3	8
	2	37	2	4	2	2	2	2
	1	6	1	0	1	0	1	0
	0	51	0	4	0	1	0	3
	Unknown	6	death	1	death	1	unknown	0
incontinence	**Grade**	**No.**	**Grade**	**No.**	**Grade**	**No.**	**Grade**	**No.**
	3	1	3	0	3	0	3	0
	2	4	2	0	2	0	2	0
	1	21	1	5	1	4	1	1
	0	83	0	13	0	2	0	11
	Unknown/ too young	20	death	1	death	1	death	0
			Unknown/ too young	2			Unknown/ too young	2

NDS: children without Down syndrome; DS: children with Down syndrome

Figure 1. Constipation according to the Krickenbeck grade.
NDS : children without Down syndrome; DS: children with Down syndrome

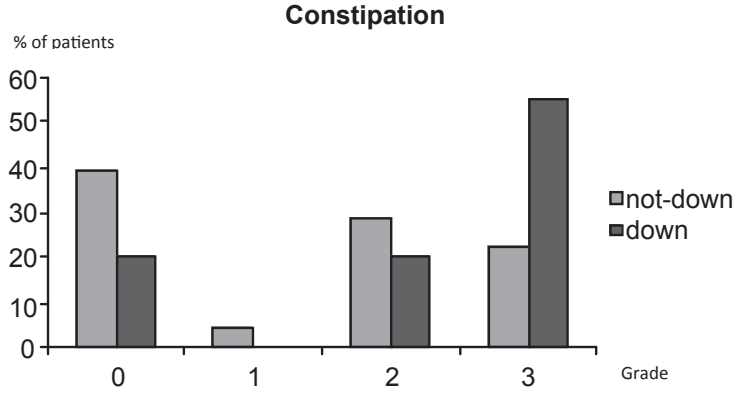
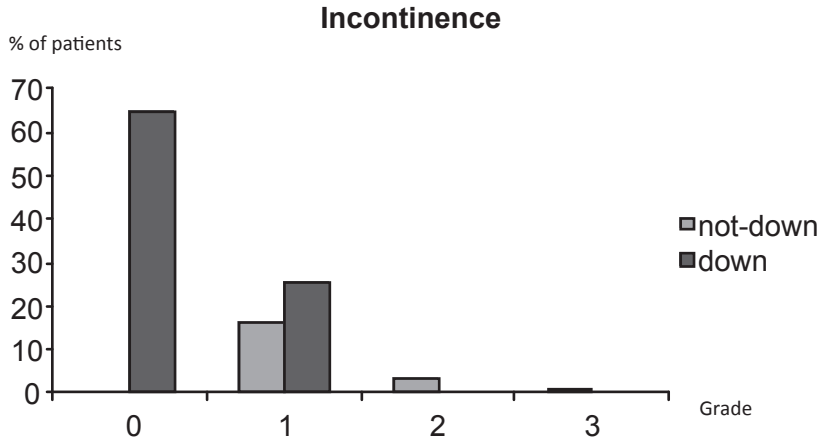


Figure 2. Incontinence according to the Krickenbeck grade.
NDS : children without Down syndrome; DS: children with Down syndrome



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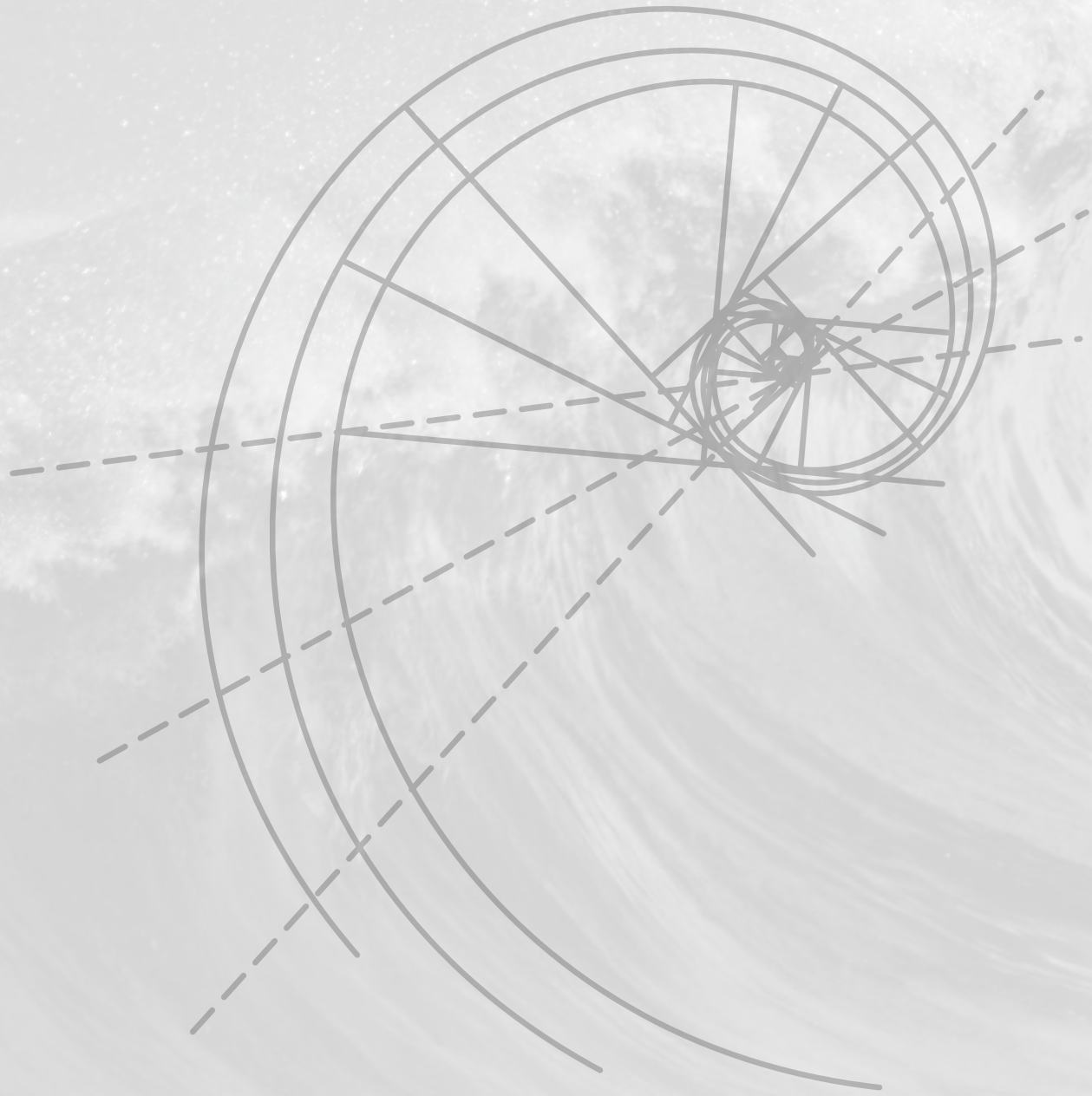

Chapter

7

Is complete resection of the aganglionic bowel in extensive total aganglionosis up the middle ileum always necessary?

Daisy Vieira Travassos[1], David C. van der Zee[1]

[1]Department Pediatric Surgery, Wilhelmina Children's Hospital, University Medical Center Utrecht, Wilhelmina Children's Hospital

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Abstract

Background/Purpose: Total colonic aganglionosis is an unusual form of Hirschsprung's disease, reflected by the small number of published case studies. The goal of this study was to analyze our cases of the last 22 years and report on our experience with 3 cases of extended total aganglionosis proximal to the middle ileum in which remaining aganglionic bowel was left in situ.

Materials and Methods: In a period of 22 years (from January 1988 to April 2010), we operated on 15 children with total aganglionosis. These children were among 163 children with Hirschsprung's disease. In 3 patients with extended aganglionosis proximal to the middle ileum, remaining aganglionic bowel was left in situ. Data were collected from the medical records, including each patient's demographics, medical history, primary treatment, complications, and follow-up.

Results: Eleven of the 15 children received an ileostomy as first treat–ment, and 4 children underwent a primary Duhamel procedure. Early postoperative complications included an abscess after an open procedure in a patient with trisomy 21 syndrome and an incorrect leveling resection that required an ileostomy. There were 2 deaths at 6 and 16 months post-operatively. The mortality rate was 13.3%. Of the 15 patients, 7 (46%) presented with at least 1 episode of postoperative enterocolitis, and only 2 of these patients had more than 3 episodes. We treated 3 patients with extended aganglionosis up to midileum (20%) in which the proximal resection level was in the aganglionic segment of ileum at the level of the ileostomy. The ileostomies were shown to be functioning satisfactorily before the pull through, so going more proximal to the ileostomy might have meant that the patient would present short bowel problems. These 3 patients had good bowel function postoperatively.

Conclusion: In principle, resection of the aganglionic bowel is mandatory to relieve obstruction and subsequent complications. There are situations, however, where the complications of a short bowel begin to outweigh the benefits of resection. In these cases, leaving remaining aganglionic bowel in situ may be an advantageous option for the patients with total aganglionosis extending to the midileum whose ileostomy functions well.

Introduction

Total colonic aganglionosis is an unusual form of 45 Hirschsprung disease, comprising 5% to 15% of all cases 46 of Hirschsprung's disease [1, 2]. It is also well known that in this patient group, the morbidity and mortality are higher than that in the classic form of Hirschsprung disease [1, 3-5]. It is generally accepted that the entire aganglionic bowel should be removed to avoid motility-related morbidity [6]. The goal of this study was to analyze our cases in the last 22 years, focusing on 3 cases of extended total aganglionosis proximal to the middle ileum in which remaining aganglionic bowel was left in situ.

1. Patients

Over a period of 22 years (January 1998 to April 2010), we operated on 163 children with Hirschsprung's disease, of which 15 (9.2% incidence) had total aganglionosis. Male-to- female ratio was 12 to 3 patients (Table 1). In 3 patients, total aganglionosis was extended up to the middle ileum. In all 3 cases, aganglionic bowel remained in situ postresection. Three patients were preterm (34, 34, and 35 weeks of gestation). The birth weight ranged from 1.9 to 4.0 kg (Table 1).

1.1. Associated anomalies

One patient had translocation of chromosome 20/21, 1 child had Waardenburg syndrome, and another had trisomy 21 syndrome with duodenal atresia.

1.2. Family history

In our patient population, there were 2 brothers from one family, in which a third brother had died earlier from Hirschsprung disease. This boy was, however, not treated in our hospital. The father of the boy with Waardenburg syndrome is deaf. The girl with chromosome 20/21 translocation inherited this from her mother.

2. Materials and methods

Clinical records were reviewed to evaluate the postoperative complications and long-term follow-up according to the standards and practices of the Dutch Society of Pediatric Surgery.

Total aganglionosis was defined as aganglionic involvement of the entire colon with or without extension into the small intestine. Extended aganglionosis was defined as extending to the mid–small bowel [7].
The criteria for diagnosing enterocolitis were patient admission for episodes of diarrhea and general illness, with or without fever and abdominal distension. Continence was only evaluated above the age of 4 years.
Statistical analysis was not performed because of the limited number of patients.

3. Results

3.1. Symptoms of presentation

Nine patients presented with bilious vomiting, 3 patients with constipation, and 2 with a distended abdomen. One patient presented with necrotizing enterocolitis associated with prematurity. In 12 patients, the diagnosis was made in the first week of life, and 3 others were diagnosed at days 49, 63, and 84 of life.

3.2. Treatment

Eight children underwent an open Duhamel procedure, and 7 had a laparoscopic Duhamel procedure. Seven children were operated on before 1994, the point at which we started using the laparoscopic procedure. One patient with Down syndrome was submitted to an open procedure in 2001 because of his history of multiple laparotomies and adhesions.
Most of the children (11) received an ileostomy as first treatment. Three were initially managed with rectal washouts, but one child did not respond to washouts; therefore, subsequently, an ileostomy was necessary. One child received total parenteral nutrition before having the Duhamel procedure. All ileostomies were closed during the Duhamel procedure, with the exception of 1 patient who received a new protective ileostomy after an open Duhamel procedure (1988).
The age of the patients who had the Duhamel procedure ranged from one to 16 months (median, four months). The weight ranged from 2.5 to 11 kg (median, 5.0 kg).

3.3. Postoperative stay

The postoperative hospital stay ranged from seven to 173 days (median, 13 days; mean, 33 days). Increased length of hospital stay was primarily caused by feeding intolerance, diarrhea, the need for total parenteral

nutrition, and complications such as jaundice and intravenous catheter sepsis.

3.4. Early complications

One patient with trisomy 21 syndrome developed an intra-abdominal abscess in the postoperative course of an open procedure (Table 2).
One child underwent a laparotomy five days after a laparoscopic Duhamel procedure because of a suspected low intestinal obstruction; this was not confirmed during the operation. Another child had an ileostomy on the seventh postoperative day because of an incorrect resection at the level of the ascending colon as shown in the definitive pathology. The pathologist initially observed ganglion cells in the frozen sections of the ascending colon leading the resection to this level, but the definitive analysis of the postoperative pathological examination demonstrated aganglionosis of the proximal resected bowel. The redo-Duhamel procedure was performed in an open approach, 15 months after the first Duhamel procedure.

3.5. Late complications

Mortality

There were two deaths. One patient who underwent an open procedure in 1988 died 16 months after the operation in another hospital. It was believed that acute dehydration caused by enterocolitis was the cause of death. The second case of death was unknown and occurred suddenly at home 6 months after a laparoscopic procedure. An autopsy was not performed. This patient had had residual aganglionosis on the proximal resected bowel and had had daily rectal washouts for defecation. Between the time of Duhamel procedure and the time of death, he had not had any episode of enterocolitis (Table 2).
The total mortality rate was 13.3%.

Perianal dermatitis

Twelve of the 15 patients initially presented with perianal dermatitis. This was managed conservatively, and the problem tended to decrease over time in all patients except for one girl whose parents were not able to manage the problem; this patient was given an ileostomy four years after the Duhamel procedure.

Adhesive intestinal obstruction

One patient, after an open Duhamel procedure, had obstructive ileus 2 times and underwent a laparotomy 9 and 11 years, respectively, after the Duhamel operation.

Enterocolitis

Of the 15 patients, 7 (46%) experienced at least 1 episode of postoperative enterocolitis. Only 2 patients had more than 3 episodes. The first patient had 11 episodes of enterocolitis after an open Duhamel procedure, 10 of which were more than 1 year after the operation. The second patient had 9 episodes of enterocolitis after a laparoscopic Duhamel procedure, with 7 of those episodes taking place more than 1 year postoperatively (Fig. 1).

Bowel function/continence results

Of the 15 patients, 6 have regular intestinal movements with a frequency of 3 to 5 defecations daily. Two patients require Imodium (loperamide hydrochloride) to treat diarrhea. Three patients needed rectal tubes to enable defecation. These patients probably were "hyper continent" (Fig. 2).

One patient had an ileostomy caused by serious perianal dermatitis 4 years after a Duhamel procedure, but this patient was continent before undergoing ileostomy.

None of the patients are incontinent. One patient has still occasional soiling after a 14-year follow-up. In 5 patients, continence could not be evaluated: 1 patient who is 1 year old now is not yet at an age to evaluate continence (4 years). Two others have died, and 1 patient is living abroad. Continence also could not be evaluated in the patient with translocation of the chromosome 20/21. This patient has mental retardation and, although she is now 4 years old, has not been toilet trained yet.

3.6. Aganglionic bowel left in situ in patients with up to midileum involvement

We had 3 patients with extended aganglionosis up until the midileum (20%) in which the proximal resection level was either in the aganglionic segment of ileum at the level of the ileostomy or somewhat proximal to the ileostomy. The ileostomies had been functioning satisfactorily before the pull through, and going more proximal to the resection could mean that the patient would experience short bowel problems. In those 3 patients,

it was not determined exactly how far the aganglionosis reached because we did not persist in performing biopsies until ganglions could be found. In 1 of the patients, the ileostomy was positive for ganglion cells when pathological examination was performed at the time the ileostomy was placed; however, at the time of the Duhamel pull through, the ileostomy proved to be aganglionic. The 3 patients had good bowel function postoperatively. One patient who is still doing well after a 4-year follow-up has experienced one episode of enterocolitis about 6 months after the pull-through operation. The second patient died at the age of 6 months, suddenly at home without apparent cause. He was seen about 10 days before his death in our outpatient clinic and had, at the time, no obvious complaints. Unfortunately, no autopsy was performed. The third patient is doing well after a 10-month follow-up and so far has not presented with enterocolitis. All 3 patients have dilated bowel loops on abdominal x-ray as in most patients with short bowel; however, physical examination revealed no extensive abdominal wall distension. In 1 patient, we performed a contrast study at the time of presentation with an episode of enterocolitis. This confirmed the presence of dilated small bowel without stenosis or caliber difference of the small bowel loops (Table 3).

4. Discussion

Total colonic aganglionosis is a rare variant of Hirschsprung disease with an incidence of 5% to 15% of all cases of Hirschsprung disease [2, 4]. Most case studies published are limited, with the exception of an extensive series of case studies published by Ieiri et al. [3] based on a Japanese nationwide survey including 343 patients. This study was important in generating mainly outcome data.

The mortality rate of total colonic aganglionosis is relatively high compared with the classic form of Hirschsprung's disease. Ieiri et al. [3] showed a decrease in mortality between 1978 and 2002 from 40.9% to 15.8%. We have published a review of 55 cases of classic Hirschsprung's disease with a mortality of 0% [8], and the mortality rate in our current series of total aganglionosis cases is 13.3%. Marquez et al. [1], in a comprehensive review, showed a mortality rate of 1.9% after the definitive operation.

Cheung et al. [9] published a review of 10 cases in 18 years in which 4 patients were submitted to 1-stage procedure at a mean age of 27

days. According to this author and Wildhaber et al. [5], the concerns in performing 1-stage pull through in total colonic aganglionosis include the possibility of incorrect leveling of the aganglionic segment and the inability to adapt to the more rapid transit time resulting in perianal excoriation. We performed 4 one-stage Duhamel procedures and 3 open and 1 laparoscopic procedures. Two of these had no postoperative perianal excoriation, and in 1 patient, it was not possible to observe this problem because he had an ileostomy on the seventh postoperative day after an incorrect leveling resection. In this specific case of 1-stage laparoscopic procedure, the resection performed at ascending colon level was incorrect, confirming literature findings.

Perianal dermatitis is one of the most common complications of pull-through operations [4, 5, 9] and tends to lessen in severity in time. In our series, we had one exceptional case in which the problem was not manageable and the patient was given an ileostomy 4 years after the pull through. We observed that 20% of the patients (3 patients) required anal dilatation or tubes to achieve defecation during the first months after the pull through. This problem also tends to improve with time, and we defined this as "hypercontinence." Our patients presented no stenosis. Various authors describe similar observations: Wildhaber et al. [5] mentioned that in their series, 25% of the patients needed anal dilatation, which they described as anal stricture. Marquez et al. [1] diagnosed these problems as internal sphincter spasm.

The incidence of enterocolitis in total aganglionosis is higher than that in classic Hirschsprung's disease, ranging from 30% to 75% [1, 4, 5]. We describe an incidence of 46%, which is higher than the incidence of 21.8% in our classic Hirschsprung disease cases as previously published [8].

The proximal extent of the aganglionosis is the terminal ileum in approximately 75% of the cases, the midileum in 20%, and the jejunum in 5% [10]. Mauricio et al. [4] had a 22% incidence of midileum involvement. In 3 cases (20%), we encountered midileum involvement.

It is generally accepted that leaving the aganglionic bowel is associated with a poor outcome [6, 5, and 11]. Most of the patients require a reoperation. We corroborate this general finding in situations where the aganglionosis extends more distally than the middle ileum, as detailed in the case of the patient who, because of incorrect leveling at the ascending colon, required a re-resection.

Alternatively, one of the major problems concerning the total colonic

aganglionosis extending to the proximal small intestine is short bowel syndrome and, therefore, the necessity for long-term total parenteral nutrition with its related complications, or even the indication for bowel transplantation [4]. According to the review publication by Ieiri et al. [3], the most frequent cause of death was sepsis, followed by hepatic failure after long-term parenteral nutrition and disseminated intravascular coagulation. Even with the recent decrease in mortality rate in total colonic aganglionosis, Ieiri et al. [3] showed a still high mortality rate in those cases that had small bowel involvement (35%).

Mauricio et al. [4] published a review covering 32 years of experience with 36 patients in which 8 patients developed short bowel and 6 required home total parenteral nutrition with a duration range of 3 to 14 years. In the review published by Wildhaber et al. [5], 5 of 25 patients had more extensive aganglionosis: 1 underwent an endorectal pull-through procedure, 1 underwent intestinal transplantation, and 3 patients died. In our 3 cases with midileum involvement, to avoid those complications associated with extended bowel resection and short bowel, we decided not to go much further with the resection than the level of the ileostomy, which presented as functioning well. Although 1 patient died of unknown cause, the 2 remaining patients are doing well, with regular bowel movements. If we would consider this death as related to the extended aganglionosis, the death rate by our extended aganglionosis patients will be 33.3%, which is comparable with the review published by Ieiri et al. [3] (35%). The incidence of enterocolitis did not seem to be higher than that in the other cases of total colonic aganglionosis, as only a single patient had 1 episode of enterocolitis. The 2 patients do not need long-term parenteral nutrition and have no perianal excoriations at long-term follow-up.

Although it is not possible to draw a conclusion after only 2 successfully treated cases, it would seem that leaving aganglionic bowel in situ when the resection extended to the midileum and the ileostomy is functioning well is acceptable for those patients to avoid short bowel and its complications.

In conclusion, total colonic aganglionosis is an unusual form of Hirschsprung disease, often accompanied by an increased morbidity and mortality. Resection of the aganglionic bowel is mandatory to relieve obstruction and its sequelae such as enterocolitis. There is, however, at some point a moment where the balance may tip and the complications from short bowel begin to outweigh the benefits of resection. In these

cases with a well-functioning ileostomy, leaving remaining aganglionic bowel in situ maybe an advantageous option for patients with total aganglionosis extending to the midileum. The treatment of patients with extensive aganglionic small bowel still needs further study and follow-up.

Table 1: Patients characteristics

Total colonic aganglionosis (n)	**15 (3 extended up to middle ileum)**
Sex (Male: Female)	12:3
Gestational age (Mean, weeks)	38,6 (Range 34-43)
Weight of birth (Mean, kg)	2,6 (Range 1,9-4)

Associated anomalies
- Translocation Chromosome 20/21
- Waardenburg's syndrome
- Trisomy 21 and duodenal atresia

Family history
- Mother with Chromosome 20/21 Translocation
- Father with Waardenburg syndrome/ deafness
- 3 brothers with total aganglionic colon

Table 2: Complications

Early complications	
Abscess in Trisomy 21 patient	
Exploratory laparotomy in suspected obstruction	
Obstruction in incorrect levelling resection at the ascending colon	
Late complications	
Deaths	2 patients • Possible dehydration in enterocolitis • Possible suddenly infant death
Perianal dermatitis	12 patients (1 ileostomy)
Adhesive intestinal obstruction	1 patient (2 times)
Enterocolitis	7 patients

Figure 1: Follow up / episodes of enterocolitis

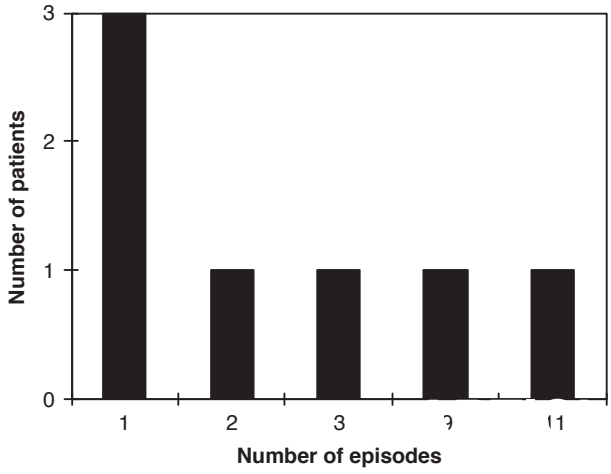

Figure 2: Follow up /bowel function

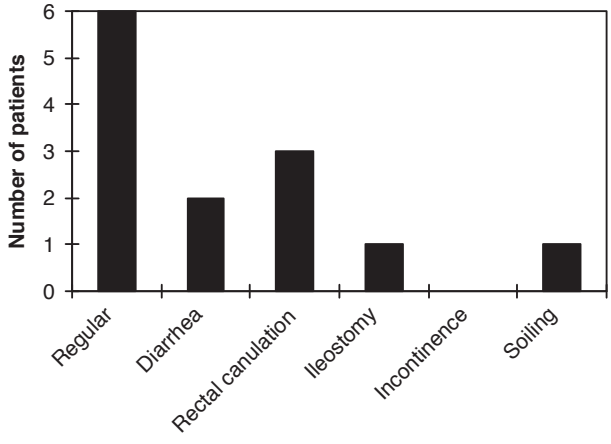

Table 3 Overview of aganglionic bowel left in situ cases

	Case no. (year)		
	Case 1 (2006)	Case 2 (2008)	Case 3 (2010)
Preoperative ileostomy	Good function	Good function	Good function
Resection level	Up to middle ileum	Up to middle ileum	Up to middle ileum
Histology at the resection level	Complete aganglionic	Complete aganglionic	Complete aganglionic
Postoperative perianal dermatitis	Temporary	No	Temporary
Postoperative washouts	Temporary	Yes	Temporary
Postoperative enterocolitis	1 episode	No episodes	No episodes
Small bowel dilatation	Yes	Yes	Yes
Death	No	Yes	No

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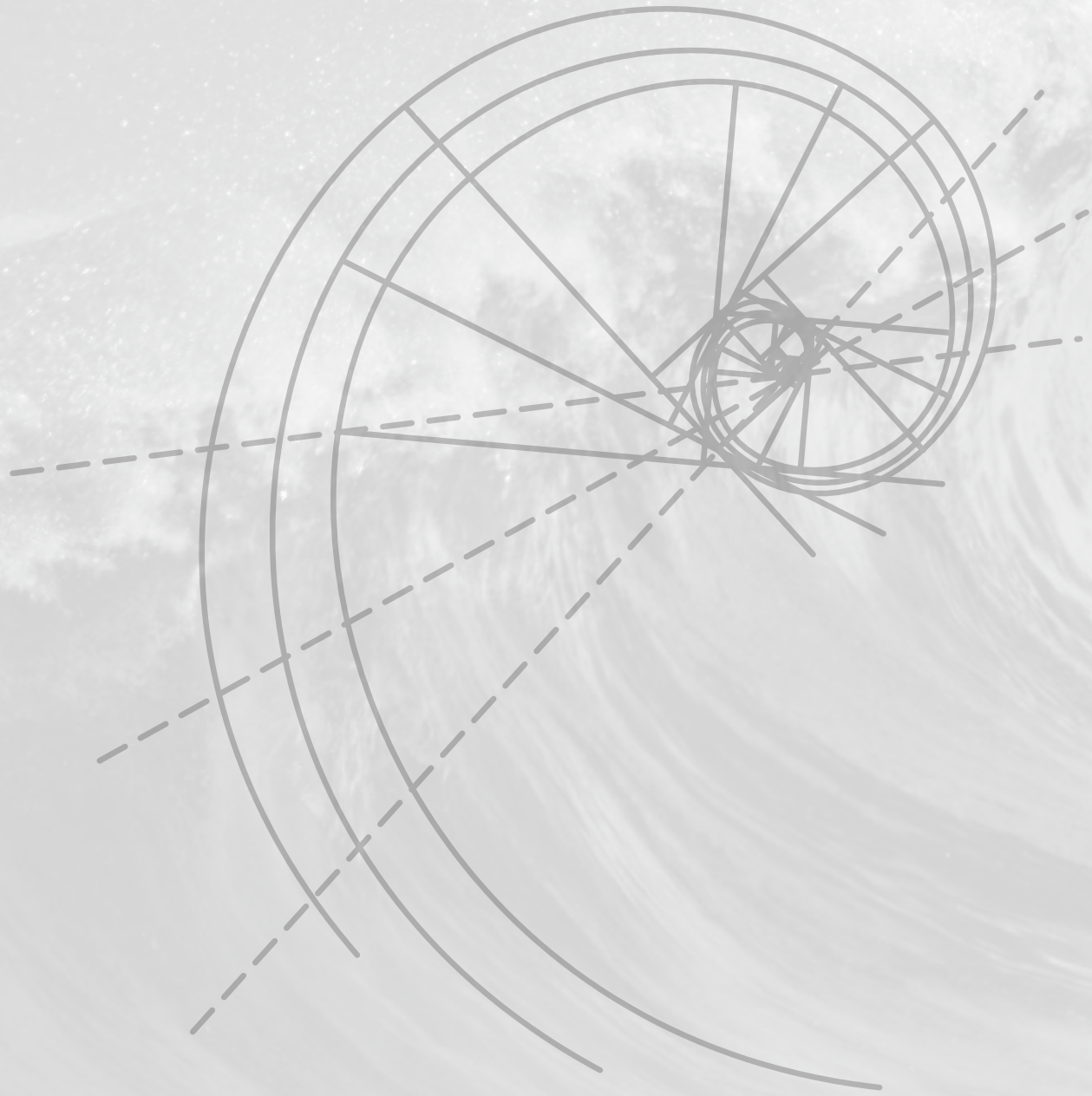

Chapter

8

General discussion

Discussion of the results

Hirschsprung's disease is not curable yet. All the different operative methods currently used, leave a small segment of aganglionic bowel behind. Since the bowel is affected from the internal sphincter towards proximally in variable extension, a complete resection of the entire affected bowel would mean that the patient would become incontinent, which is unacceptable. [1]
The surgical treatment of Hirschsprung's disease limits the complications, morbidity and mortality related to the disease but does not restore the underlying disorder, namely the replacement of the neurons of the Enteric Nervous System. The only hope to cure Hirschsprung's disease in the future will be stem cell transplantation to replace the missing neuronal cells of the bowel. Stem cell transplantation for gut motility disorders and Hirschsprung's disease is indeed promising, but is currently in an experimental phase and right now unrealistic for clinical application.[2] Until a curative treatment will become available, the affected patients with Hirschsprung's disease may not escape from the surgeon's knife for palliative treatment. As the surgical treatment for Hirschsprung's disease is a palliative therapy, it has limitations and is far from being ideal. This is probably the reason why several surgical techniques are available to treat Hirschsprung's disease. Nevertheless, the response to the surgical therapy is often not satisfactory. It is quite common that children despite an operative treatment for Hirschsprung's disease keep presenting with defecation disorders such as chronic constipation, soiling, incontinence and enterocolitis.[3] Different aspects may be involved in the cause of persisting motility and defecation disorders after the surgical treatment for Hirschsprung's disease, some of which have been discussed in this thesis.

Concerning the preoperative diagnostic studies and different types of intestinal innervation disorders

In our preoperative intestinal transit time study (Chapter 3), we found that 100% of the children with Hirschsprung's disease have delayed intestinal transit time preoperatively. Also 50% of the children with neuronal intestinal dysplasia (NID type B) and 87,5% of the children with hypoganglionosis had delayed transit time. In this study, all children

with aganglionosis and all the hypoganglionosis cases with delayed intestinal transit time were submitted to resection. No children with normal transit time required operation. The postoperative transit time was not evaluated. Miele et al. [4] has investigated the intestinal transit time after operation for Hirschsprung's disease in 22 patients and found that all transit time measurements, gastric, colonic and total gut to be longer in children operated for Hirschsprung's disease. It seems that the intestinal motility disorder can not be solved with the resection of the aganglionic segment alone, because the motility disorder may extend beyond the margin of the aganglionic bowel self.

The absence of the rectoanal inhibitory reflex persists after surgery. [4,5]. This may be the explanation why some children seem to be "hypercontinent" requiring rectal canulation to achieve defecation after resection of the aganglionic bowel.

The presence or absence of allied neuronal intestinal malformations may play a role in the preoperative symptoms and postoperative outcome after surgery for Hirschsprung's disease. In the chapter 2, analyzing the clinical impact of the intestinal malformations 75% of the patients with aganglionosis and associated NID B presented preoperatively with an obstructive ileus, in contrast to 32,5% of the patients with isolated aganglionosis. Furthermore, six of the seven patients requiring re-resection after surgery for Hirschsprung's disease had associated NID B. Seven of the nine patients with hypoganglionosis required resection, two of them required a re-resections showing that hypoganglionosis can be clinically as relevant as Hirschsprung's disease it self. It is well known that proximal to the aganglionic bowel, there is a transitional zone that may extend as far as a 10 cm. Patients whose resection is at the transitional zone may persist to be constipated postoperatively. The clinical implication of neuronal intestinal dysplasia is an ongoing subject of debate between the pathologists, pediatric surgeons and pediatricians. Schmittenbecher et al. (1999) [6] prospectively analyzing the association between Hirschsprung's disease and neuronal intestinal dysplasia at 10 pediatric surgery departments in central Europe found a 40% incidence of association of the two pathological findings. After resection for Hirschsprung's disease, they found a constipation rate of 40% in patients with associated disseminated NID B, compared to 20,6% in patients with isolated Hirschsprung's disease. Fadda et al. (2011) [7] found 44% incidence of NID B in the proximal resected segment among his patient group operated for Hirschsprung's disease. The North

American literature is quite skeptical concerning the diagnosis of NID B, which is mostly described in Europe. [9,10]
The knowledge about NID B has progressed since it was first described by Meier-Ruge in 1971 [11] but there are still aspects of controversy to be clarified in the future. The criteria for the diagnosis have changed recently: the diagnosis should only be made after the age of one year, because earlier in life giant ganglia can be present in asymptomatic patients. Bruder and Meier-Ruge in 2007 [8] published a review on neuronal intestinal dysplasia in which they suggested that by using the current diagnostic criteria to diagnose NID B after one year of age, NID B becomes more uncommon than firstly thought. The diagnosis is then reasonable in only 6% of the patients with Hirschsprung's disease and 2,9% of the children with persistent constipation after the age of one year. Until the age of four years the clinical and morphological findings of NID B may resolve spontaneously but can persist in a small amount of children. Therefore conservative treatment is recommended. Since most patients are operated for Hirschsprung's disease in the first months of life, it has become more complex to determine the "new" incidence of neuronal intestinal dysplasia in the proximal resected segment of bowel from these patients and to link it to the postoperative bowel function. The 27,79% incidence of NID B in the proximal segment of Hirschsprung's disease as we showed in the chapter 4 may be much lower under the new criteria for the diagnosis of NID B after the age of one year. Anyway, the clinical relevance concerning postoperative constipation would not change significantly because the constipation rate by children with NID B in the proximal segment was just slightly higher than in children with regular histological patterns in the proximal segment (17,8% versus 10,5%). However, the difference was not significant. In summary recent insights have led to the conclusion that NID B plays only a limited role in postoperative constipation in Hirschsprung's disease after the age of one year.

Open versus laparoscopic procedure

The introduction of laparoscopic techniques awakened the curiosity to compare this to the open procedure: Is the laparoscopic procedure as safe as the open procedure? Are the complication rates higher? Is the time to first oral feeding, length of the postoperative stay shorter? Is the long-term follow up outcome similar or even better? How about the cosmetic results?

In our comparison between the laparoscopic and open Duhamel procedure (chapter 5) we found no significant differences between the open and laparoscopic techniques concerning the complications and functional outcome. We found no cases of postoperative adhesive obstruction in the laparoscopic group versus three cases of obstructive adhesions in the open group. The difference is not statistically significant but the group size was small. Our findings are supported by other authors who found no major differences when comparing open with laparoscopic techniques, irrespective the technique they used. [12,13,14] According to Fujiwara [13] the laparoscopic-assisted pull-through approach is superior to the open pull-through (Georgeson's technique [15]) concerning fecal continence. He stated that when dividing the vascularization of the colon under laparoscopic control, excessive stretching of the anal canal to reach the proximal colon as usual in the open pull-through can be avoided. As this excessive stretching of the anal canal is not necessary in the Duhamel technique, in our comparison between open and laparoscopic techniques we have not observed any case of incontinence in both, laparoscopic and open, groups. There is no doubt that with smaller incisions the patients have less postoperative pain and recover more quickly. The better cosmetic results of the laparoscopic approach can be important for the self-confidence/ esteem of the patients in the adolescence and adulthood. It would be interesting to compare the impact of cosmetic results between the laparoscopic and open groups after achieving the age of adolescence. In conclusion there are no disadvantages of laparoscopic over open repair of Hirschsprung's disease. Postoperative complications tend to be less and cosmesis is better in the laparoscopic approach.

Specific groups of patients with Hirschsprung's disease

Hirschsprung's disease and Down syndrome (Chapter 6)

About 13% of the children with Hirschsprung's disease have associated Down syndrome; patients with Down syndrome have a higher risk to be affected by Hirschsprung's disease than the general population. This group of patients was analyzed separately to display the difference between the outcome of patients with and without Down syndrome. Down syndrome is associated with defects of the immune system predisposing these children to infectious complications when submitted to surgery. We found a higher incidence of anastomotic leakage and abscess

formation in the early postoperative period as well a higher incidence of enterocolits at follow-up in children with Down syndrome than in the non-Down syndrome children. Furthermore, children with Down syndrome tend to become more severely constipated than the non-Down syndrome children.
In conclusion children with Down syndrome are not only more susceptible to Hirschsprung's disease, they also tend to be more vulnerable to complications and postoperative constipation.

Total aganglionosis (Chapter 7)

Total aganglionosis is also a distinct group of Hirschsprung's disease. The incidence varies from 5% to 15% of all cases of Hirschsprung's disease. This group tends to present a higher morbidity and mortality rate than classical Hirschsprung's disease as well to present problems related to extensive bowel resection such as diarrhea, perineal excoriation and short bowel syndrome. The proximal level of the aganglionosis when reaching the small bowel is the terminal ileum in approximately 75%, the mid ileum in 20% and jejunum in 5% of cases. According to the principles of the surgical management of Hirschsprung's disease, the entire aganglionic bowel should be resected to avoid the persistence of bowel obstruction symptoms and enterocolitis. Patients with residual aganglionosis in the colon after pull-through operation show persistence of constipation and require re-resection. [16] In three cases of extended aganglionosis up to the mid ileum, in which the aganglionic ileostomy was functioning well, we did not remove the complete aganglionic small bowel in order to avoid short bowel complications. The patients achieved satisfactory postoperative bowel function and did not have a higher incidence of enterocolitis than the other cases of total aganglionosis. One of the three patients died from an unknown cause. It can be attributed to sudden infant death or it could be due to congenital central hypoventilation syndrome, which can be related to Hirschsprung's disease. It seems that the extended aganglionosis differs from the classical Hirschsprung's disease in the sense that the extensive bowel resection required to treat the aganglionosis may compensate the bowel motility disorder caused by the residual aganglionosis. In other words, the more extensive the resection is, the less important the effects of the histological patterns of the proximal segment may become. In our study about the proximal segment histology in Hirschsprung's disease (Chapter 4) we observed that the histological findings in the proximal

segment became less important whenever an extensive colon resection was indicated. Of those who required a transversorectostomy or an even more extensive colon resection, 72,1% had regular bowel function although only one third of them (32,3%) had normal proximal segment histology. Leaving of aganglionic bowel when the aganglionic ileostomy function well is a novel alternative in the treatment of extended total aganglionosis that requires further studies.
In conclusion children with total aganglionic colon are exposed to more complications such as diarrhea, perineal excoriation and short bowel.
Resection of the affected bowel is mandatory. However, if the disease extends up to the mid-ileum or more, complications due to short bowel may tip the balance, and when the aganglionic ileostomy is functioning well, it may be considered to leave residual tissue in place.

Conclusion

Different aspects concerning the postoperative outcome in Hirschsprung's disease have been discussed in this thesis, but the mystery of why a satisfactory result can not always be reached despite operative treatment is not completely solved.
We have learned that the proximal end of the resected specimen may tell us something about the functional outcome of Hirschsprung's disease and that NID B plays only a minor role in the functional results in children over the age of one year.
The laparoscopic approach to surgical management has no adverse effects and it is likely that cosmesis will become a key player in favor of laparoscopy in the future.
Special subgroups like patients with Down syndrome or total aganglionic colon will need special attention and concentration in specialized centers is highly desirable. Also aganglionosis extending into the ileum may benefit from leaving residual tissue in place, when the aganglionic ileostomy is functioning well, in order to prevent short bowel syndrome.
So far Hirschsprung's disease has proven to be a not curable complex entity and there is still a lot to be learned and researched in order to achieve the best possible results for our patients.

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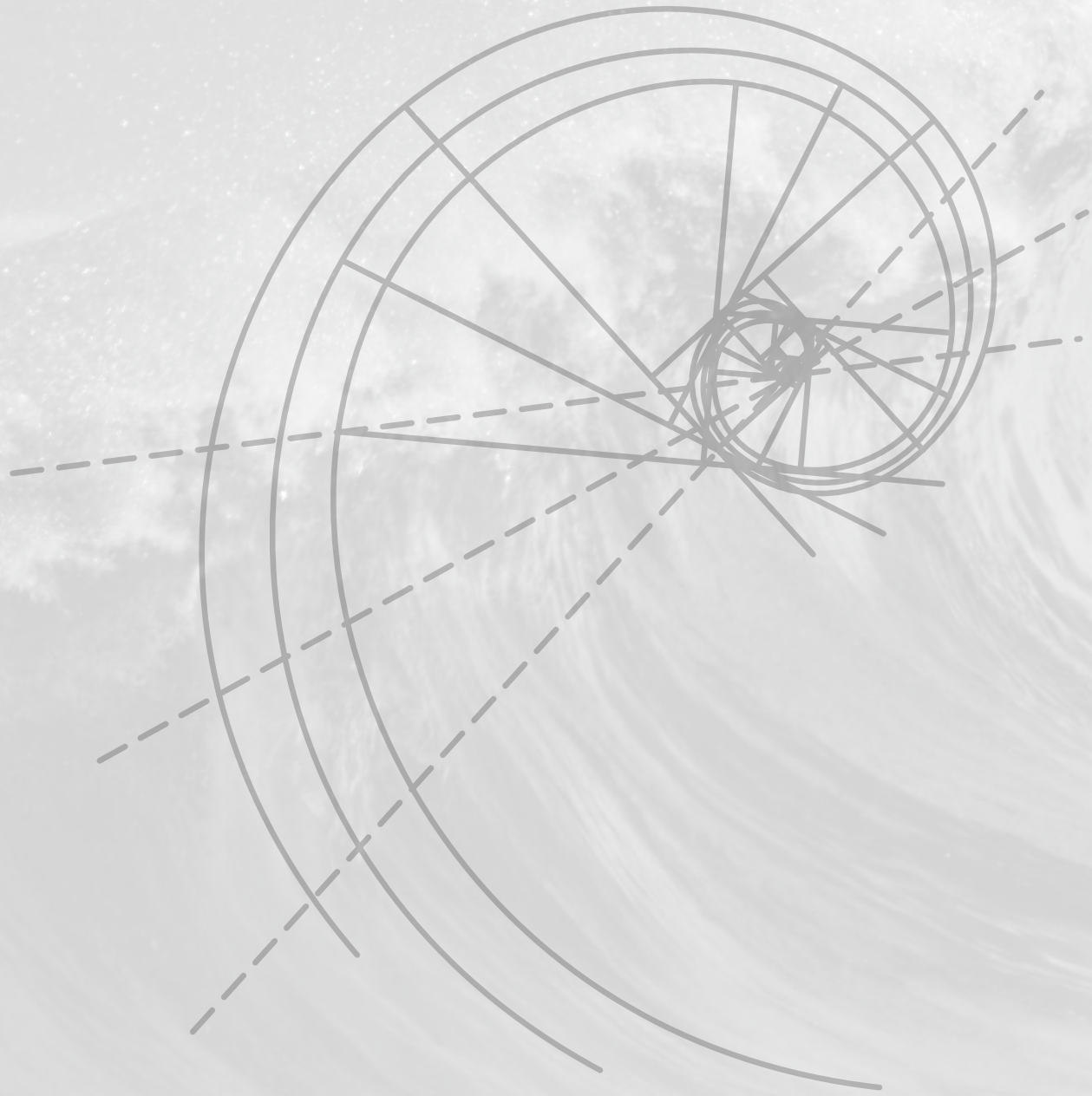


English summary

Introduction: Hirschsprung's disease is an important subject in pediatric surgery. It is an important cause of intestinal obstruction or constipation in newborns and children. It is characterized by lack of ganglion cells extending from distal in the internal anal sphincter to proximal in the colon or small bowel for a variable distance caused by arrest of migration of the ganglion cells from the neural crest. The extension of the aganglionosis is the rectosigmoid in 80% of cases, the left colon in 11% to 26% and the entire colon in 5% to 15%. Hirschsprung's disease is not curable and all the different operative methods currently used leave a small segment of aganglionic bowel behind.
The surgical treatment of Hirschsprung's disease limits the complications, morbidity and mortality related to the disease but does not restore the underlying disorder, namely the replacement of the neurons of the Enteric Nervous System. It is quite common that children despite an operative treatment for Hirschsprung's disease keep presenting with defecation disorders such as chronic constipation, soiling, incontinence and enterocolitis. This thesis analyses different aspects that could be involved in the cause of persisting motility and defecation disorders before and after the surgical treatment for Hirschsprung's disease.

Chapter 2. Clinical impact of intestinal neuronal malformations
141 patients diagnosed with intestinal neuronal malformations were prospectively analyzed. The diagnosis included aganglionosis, neuronal intestinal dysplasia (NID B), hypoganglionosis, immaturity of the ganglion cells, reduced parasympathetic tone, heterotopia of the submucous plexus, heterotopia of the myenteric plexus and mild dysganglionosis. Constipation was the main symptom in 83 patients (58,9%) and ileus was present in 43 children (30,5%). Among the patients with aganglionosis combined with NID B, 73,5% presented with ileus against 32,5% of the patients with isolated aganglionosis. All patients with aganglionosis required resection as well seven from nine children with hypoganglionosis. Of the seven children with aganglionosis that required re-resection (9,6%), 6 had combined NID B and 1 isolated aganglionosis. Among patients with NID B, one required resection and afterwards the same patient had a re- resection and two were treated by colostomy that was subsequently closed without further resection.
At the follow up of 2,4±1,4 years, 69% of the patients who underwent resection for isolated aganglionosis had normal bowel movements. No significant difference was found with the group of patients with associated NID B.

Of 66 patients without aganglionosis, 29 (43,9%) were asymptomatic at follow up. Of the 12 without aganglionosis who underwent resections, 4 (33%) had normal bowel movements, significantly less than the 69% of patients with resections for aganglionosis (P > 0,05). This was due the unfavorable results in patients with hypoganglionosis. It is concluded that some neuronal intestinal malformations may have a relevant clinical impact. Meanwhile new insight have learned us that the relevance of NID B is limited to children older than one year of age, while in most cases the diagnosis of Hirschsprung's disease is made before the age of one year.

Chapter 3. Transit time studies were performed in 106 children with diverse types of neuronal intestinal malformations.
The transit time was prolonged in all 53 patients with aganglionosis and in 37 (69,8%) of children with other neuronal intestinal malformations. Abnormal transit time was found in 50% of the NID B cases (eight of 16), in seven out eight (87,5%) of hypoganglionosis, in nine of 10 (90%) of the children with reduced parasympathetic tone and both children with heterotopia of the myenteric plexus. Only 11 of the 17 with the remainder neuronal intestinal anomalies had prolonged transit time. All children with aganglionosis and all the hypoganglionosis cases with delayed intestinal transit time were submitted to resection. No children with normal transit time required operation. The determination of the intestinal transit time represents an important tool to identify the clinical relevance of histological findings in the individual patient.

Chapter 4. The proximal segment histology of the resected bowel from 101 patients operated for Hirschsprung's disease by Rehbein procedure at the Children's Hospital, Cologne, Germany, was analyzed and the findings correlated to the postoperative bowel function.
Regular histological patterns were found in 38 cases (37,6%), those had a constipation rate of 10,5%. Neuronal intestinal dysplasia was found in 28 cases (27,7%) with a slightly higher constipation rate of 17,8%. Hypoganglionosis of the proximal segment was found in 26 cases (25,7%) with a constipation rate of 23,1%. All 4 patients with aganglionosis of the proximal segment experienced serious postoperative problems, two required re-resection, one had recurrent episodes of enterocolitis and the last patient died. A general observation of this study was that histological findings in the proximal segment became less important whenever an extensive colon resection was performed. Of those who required a

transversorectostomy or an even more extensive colon resection, 72,1% were observed to have regular bowel function although only one third of them (32,3%) had normal proximal segment histology. In conclusion, there is a link between the histological findings at the proximal resected segment and the bowel function but the histological findings of the proximal segment becomes less important whenever a more extensive resection than left hemicolectomy is required.

Chapter 5. Presents a comparative study between the patients submitted to an open Duhamel procedure (N=25) and laparoscopic Duhamel procedure (N=30) at the Wilhelmina Children's Hospital, Utrecht.

To achieve homogeneity between the two groups, patients with extended aganglionosis, pre- Duhamel ostomy or syndrome were excluded. End points were intraoperative complications, postoperative complications, time to first feeding, hospital stay, and outcome at follow up. There were no intraoperative complications in either group. No significant differences at the follow-up were observed but there was a tendency for a higher enterocolitis rate in the laparoscopic group. There was no adhesive obstruction in the laparoscopic group in contrast to three in the open group. Fecal incontinence was not encountered in either group. Except for a significantly shorter hospital stay and shorter time to first oral feeds in favor of laparoscopic Duhamel, no significant differences could be observed. The cosmetic result was not an end point but there was no doubt that it was better in the laparoscopic group.

Chapter 6. Hirschsprung's Disease in Children with Down Syndrome: a comparative study

Among 149 children operated on for Hischsprung's disease in the period between 1987 and 2008 at the Wihelmina Children's Hospital, Utrecht, 20 were additionally diagnosed with Down syndrome. All the children underwent either an open or a laparoscopic Duhamel procedure. The postoperative complications and outcome of the patients, with and without Down syndrome were compared. Postoperative anastomotic leakage occurred significantly more often in children with Down syndrome (n=5, 25%) compared to children without Down syndrome (n=1, 0,7%; $p<0.0001$). Postoperative leakage-related abscess formation was higher in the Down syndrome group (n=3, 15% versus 0%). Within the Down syndrome group there was no significant difference

between open or laparoscopic Duhamel procedure concerning these postoperative complications. Postoperative stay was significantly longer in the Down syndrome group ($p<0.05$). In the Down syndrome group there was a slightly shorter hospital stay after laparoscopic Duhamel. Severe constipation was significantly more common in Down syndrome children (55 versus 22,3%). Enterocolitis occurred more frequently in Down syndrome children after operation. There was no difference in incontinence between the two groups. In conclusion: Children with Down syndrome have a higher rate of postoperative complications and a longer hospital stay. During long-term follow up most patients with Down syndrome are severely constipated and have a higher incidence of enterocolitis.

Chapter 7. Is complete resection of the aganglionic bowel in extensive total aganglionosis up the middle ileum always necessary?

Total colonic aganglionosis is an unusual form of Hirschsprung's disease, with an incidence varying from 5% to 15% of all cases of Hirschsprung's disease. It is also well known that in this patient group the morbidity and mortality is higher than in the classic form of Hirschsprung's disease. In a period of 22 years there were 15 cases operated on for total colonic aganglionosis at the Wihelmina Children's Hospital, Utrecht among 163 children with Hirschsprung's disease. The outcome of the total aganglionosis cases were analyzed concerning postoperative complications, mortality rate and follow up. Three special cases of extended total aganglionosis up to the middle ileum were presented in which aganglionic bowel was left in situ in order to avoid short bowel and its complications with satisfactory results. This possibility in the management of the extended total aganglionosis has not been reported before.

Results: The incidence of enterocolitis in total aganglionosis is higher than in classic Hischsprung's disease. We had an incidence of 46% postoperative enterocolitis, which is higher, compared to the incidence of 21,8% in our classic Hirschsprung's disease cases published before. Perianal dermatitis is one of the most common post pull-through complications that tend to decrease with time. Twelve of the 15 patients presented temporary perianal dermatitis. In our series we had one exceptional case in which the problem was not manageable and the patient was given an ileostomy four years post pull-through. The mortality rate is relatively high compared to the classic form of Hirschsprung's

disease. We have published a review of 55 cases of classic Hirschsprung's disease with a mortality of 0%. The mortality rate in our current series of total aganglionosis cases is 13,3%. The upper border of aganglionosis extending into the small bowel is the terminal ileum in 75% of the cases, the mid-ileum in 20% and the jejunum in 5%. In three cases with mid-ileum involvement we decided not to go much further with the resection than the level of the well functioning but aganglionic ileostomy in order to prevent short bowel complications associated with extensive bowel resection. One patient died of unknown cause; it can be speculated to be due to congenital central hypoventilation syndrome which is known to be related to Hirschsprung's disease. The two remaining patients are doing well, with regular bowel movements. The incidence of enterocolitis did not seem to be higher than in the other cases of total colonic aganglionosis since just one patient had one episode of enterocolitis. The two patients do not need long term parenteral nutrition and have no perianal excoriations at long-term follow-up.
In conclusion total colonic aganglionosis is an unusual form of Hirschsprung's disease, often accompanied by an increased morbidity and mortality. Resection of the aganglionic bowel is mandatory to relieve obstruction and its sequelae such as enterocolitis. There is, however, at some point a moment where the balance may tip and the complications from short bowel begin to outweigh the benefit of resection. In these cases with a well functioning but aganglionic ileostomy, leaving remaining aganglionic bowel in situ may be an advantageous option for patients with total aganglionosis extending to the mid-ileum. The treatment of patients with extensive aganglionic small bowel still needs further study and follow-up.

Discussion: Many different aspects may be involved in the causes of persisting motility and defecation disorders after the surgical treatment for Hirschsprung's disease such as the presence of associated neuronal intestinal malformation in the resected and remaining bowel. We could find a link between the histological findings at the proximal resected bowel and the postoperative outcome. The patients with aganglionosis and hypoganglionosis at the proximal remaining bowel have more chances to present defecation problems than patients with regular histology. The patients with neuronal intestinal dysplasia (NID B) have slightly higher chances to become constipated that tend to improve until the age of four years. We also observed that the more the more extended

the resection is, the less important becomes the histological findings of the proximal segment concerning the postoperative outcome. The criteria for the diagnosis of NID B have changed recently: the diagnosis should be determined after the age of one year, because earlier in life giant ganglia may occur in asymptomatic patients. Patients with Down syndrome and Hirschsprung's disease have more chance to present postoperative complications such as anastomotic leakage and abscess formation than the children with isolated Hirschsprung's disease. Furthermore, they have a higher constipation rate. Total aganglionosis is also a distinct group of Hirschsprung's disease. This group tends to present with a higher morbidity and mortality rate than the classical Hirschsprung's disease as well as problems related to extensive bowel resection such as diarrhea, perineal excoriation and short bowel. Cases of extended aganglionosis up to the midileum are not common enough (20% of the total aganglionosis group) to get a large experience in a single department. In three cases of extended aganglionosis until the mid ileum, in which the aganglionic ileostomy was functioning well, we did not remove the complete aganglionic small bowel in order to avoid short bowel complications. Leaving aganglionic bowel proximal of a well functioning ileostomy is a novel alternative in the treatment of extended total aganglionosis that requires further studies. Laparoscopic versus open procedure: There is no significant difference between the open and laparoscopic Duhamel procedure concerning the postoperative outcome except for shorter hospital stay, shorter time to first oral feedings and lower incidence of adhesive obstruction in favor of the laparoscopic procedure. Our findings are supported by other authors that found no major differences comparing open and laparoscopic techniques, unrelated to the kind of technique used in their institutions except by the Georgeson's technique in which the prognosis for continence seems to be superior by the laparoscopic approach.

Conclusion: Different aspects concerning postoperative outcome in Hirschsprung's disease have been discussed in this thesis but the mystery of why a satisfactory result cannot always be reached despite operative treatment is not completely solved. We have learned that the proximal end of the resected specimen may tell us something on the functional outcome of Hirschsprung's disease and that NID B plays only a minor role in the functional results in children over the age of one year. The laparoscopic approach to surgical management has no adverse

effects and likely cosmesis in the future will become a key player in favor of laparoscopy. Special subgroups like patients with Down syndrome or total aganglionic colon need special attention and concentration in specialized centers are highly desirable. Also Hirschsprung extending into the ileum in the future may benefit from leaving residual tissue in place, when the ileostomy is functioning well, in order to prevent short bowel. So far Hirschsprung's disease has proven to be a not curable complex entity and there is still a lot to be learned and researched in order to achieve the best possible results for our patients.

Nederlandse samenvatting

Inleiding:
De ziekte van Hirschsprung is één van de meest intrigerende en belangrijke aandoeningen in de kinderchirurgie. Zij wordt gekenmerkt door het ontbreken van ganglioncellen van distaal in de interne anale sfincter tot proximaal in de dikke darm of zelfs de dunne darm. De variabele afstand wordt veroorzaakt door de stagnatie van de migratie van ganglion cellen van de neurale lijst. De uitbreiding van de aganglionosis reikt in 80% van de gevallen tot in het rectosigmoïd, in 11 to 16% tot in het linker colon en in 5 tot 15% van de gevallen tot in het hele colon of zelfs tot in de dunne darm. De ziekte van Hirschsprung is niet te genezen. Alle verschillende operatieve technieken die worden gebruikt, laten op dit moment een klein segment van aganglioniare darm achter. De chirurgische behandeling van de ziekte van Hirschsprung beperkt de complicaties, morbiditeit en mortaliteit gerelateerd aan de ziekte, maar herstelt niet de onderliggende aandoening, namelijk de vervanging van de neuronen van het enterische zenuwstelsel. Het is heel gebruikelijk dat kinderen, ondanks een operatieve behandeling voor de ziekte van Hirschsprung, zich presenteren met ontlastingsproblemen, zoals chronische verstopping, soiling, incontinentie en enterocolitis.
Dit proefschrift analyseert verschillende aspecten die kunnen worden betrokken bij de oorzaken van de aanhoudende motiliteit en ontlastingproblemen voor en na de chirurgische behandeling voor de ziekte van Hirschsprung.

Hoofdstuk 2. Klinische impact van neuronale malformaties van de darm: een prospectieve studie bij 141 patiënten.
De diagnosen betroffen aganglionose, neuronale intestinale dysplasie (NID B), hypoganglionose, onrijpheid van ganglion cellen, verminderde parasympathische tonus, heterotopie van de submuceuze plexus, heterotopie van de myenterische plexus en milde dysganglionose. Obstipatie was het belangrijkste symptoom bij 83 patiënten (58,9%) en ileus was aanwezig bij 43 kinderen (30,5%). Van de patiënten met aganglionosis gecombineerd met NID B presenteerde zich 73,5% met een ileus tegen 32,5% van de patiënten met geïsoleerde aganglionosis. Alle patiënten met aganglionose ondergingen een resectie, als ook zeven van negen kinderen met hypoganglionose. Van de kinderen met aganglionose die een re-resectie nodig hadden (9,6%), waren er zes met een gecombineerde NID B en bij één een geïsoleerde aganglionose. Van de patiënten met NID B had er één resectie nodig. Dezelfde patiënt had later nog een reresectie nodig en twee werden behandeld middels een colostoma, dat vervolgens later gesloten kon worden

zonder verdere resectie. Na een follow-up van 2,4 ± 1,4 jaar had 69% van de patiënten bij wie een resectie voor geïsoleerde aganglionose was verricht een regelmatig stoelgang en was er geen significant verschil met mensen met aganglionose geassocieerd met NID B. Van de 66 patiënten zonder aganglionose waren er 29 (43,9%) asymptomatisch bij de follow-up. Van de 12 kinderen zonder aganglionose bij wie een resectie was verricht, hadden vier (33%) patiënten een normale stoelgang, aanzienlijk minder dan de 69% van de patiënten met resecties voor aganglionose (P> 0,05). Dit was het gevolg van de ongunstige resultaten bij patiënten met hypoganglionose. Geconcludeerd wordt dat enkele neuronale intestinale afwijkingen een klinisch relevant effect kunnen hebben. Ondertussen hebben nieuwe inzichten ons geleerd dat NID B eigenlijk pas na het eerste levensjaar van betekenis is, en aangezien bij de meeste kinderen de ziekte van Hirschsprung al voor het 1e levensjaar wordt gediagnosticeerd, lijkt het belang relatief.

Hoofdstuk 3. Intestinale transitie tijd bij kinderen met neuronale intestinale afwijkingen, die de ziekte van Hirschsprung nabootsen.
Transitietijd studies werden uitgevoerd bij 106 kinderen met diverse vormen van neuronale intestinale afwijkingen. De transitietijd was verlengd bij alle 53 patiënten met aganglionose en in 37 (69,8%) kinderen met andere neuronale intestinale afwijkingen. Een abnormale transitietijd werd gevonden bij 50% van de NID B-gevallen (acht van 16), even van acht (87,5%) kinderen met hypoganglionose, bij negen van 10 (90%) de kinderen met verminderde parasympathische tonus en bij de kinderen met heterotopie van de myenterische plexus. Slechts 11 van de 17 met één van de rest neuronale intestinale afwijkingen had een verlengde transitietijd. Alle kinderen met aganglionose en alle kinderen met hypoganglionose en een vertraagde intestinale transitietijd ondergingen resectie. Geen van de kinderen met een normale transitietijd hadden resectie nodig.
De bepaling van de intestinale transitietijd is een belangrijk instrument om de klinische relevantie van de histologische bevindingen in de individuele patiënt te identificeren.

Hoofdstuk 4. De histologie van het proximale segment van de gereseceerde darm bij de ziekte van Hirschsprung voorspelt de postoperatieve darmfunctie.

De histologie van het proximale segment van de verwijderde darm van 101 patiënten die geopereerd waren voor de ziekte van Hirschsprung door middel van de Rehbein procedure in de kinderkliniek, Keulen, Duitsland, werd geanalyseerd en de resultaten werden gecorreleerd aan de postoperatieve darmfunctie. Een normale histologie werd in 38 gevallen 37,6% gevonden hetgeen gepaard ging met een constipatiefrequentie van 10,5%. Neuronale intestinale dysplasie werd gevonden in 28 gevallen (27,7%) hetgeen resulteerde in een iets hogere constipatiefrequentie van 17,8%. Hypoganglionose van het proximale segment werd gevonden in 26 gevallen (25,7%) met een constipatiefrequentie van 23,1%. Alle vier patiënten met aganglionose van het proximale segment hadden ernstige postoperatieve problemen: twee moesten re-resectie ondergaan, één had terugkerende episodes van enterocolitis en de laatste patiënt overleed. Een algemene opmerking van deze studie was dat de histologische bevindingen in het proximale segment minder belangrijk werden naarmate een meer uitgebreide dikke darm resectie moest worden uitgevoerd. Bij 72,1% van de patiënten die een hemicolectomie of een nog uitgebreidere dikke darm resectie ondergingen, werd een regelmatige stoelgang waargenomen hoewel slechts 32,3% van hen een normale histologie van het proximale segment histologie hadden. Concludererend: er bestaat een verband tussen de histologische bevindingen van het proximale resectie segment en de darmwerking, maar de histologische bevindingen van het proximale segment worden minder belangrijk als er een meer uitgebreide resectie dan linker hemicolectomie nodig is.

Hoofdstuk 5. Duhamel procedure: een vergelijkende retrospectieve studie tussen een open en laparoscopische techniek.

Dit hoofdstuk presenteert een vergelijkende studie tussen patiënten die een open (N = 25) of een laparoscopische Duhamel procedure (N = 30) ondergingen in het Wilhelmina Kinderziekenhuis in Utrecht. Om homogeniteit te verkrijgen tussen de twee groepen werden de patiënten met uitgebreide aganglionose, pre-Duhamel stoma of syndroom uitgesloten. Eindpunten waren intra-operatieve complicaties, postoperatieve complicaties, tijd tot eerste voeding, verblijf in het ziekenhuis, en het resultaat bij de follow-up.

Er waren geen intra-operatieve complicaties bij beide groepen. Er werden geen significante verschillen in de follow-up waargenomen, maar er was

een tendens voor hogere enterocolitis frequentie in de laparoscopische groep. Adhesieve obstructie deed zich niet voor in de laparoscopische groep in tegenstelling tot drie in de open groep. Fecale incontinentie werd in geen van beide groepen aangetroffen.
Behalve voor een beduidend korter verblijf in het ziekenhuis en een kortere tijd tot de eerste orale voeding in het voordeel van laparoscopische Duhamel, konden geen significante verschillen worden waargenomen. Het cosmetisch resultaat was geen eindpunt, maar er bestond geen twijfel dat dit beter was in de laparoscopische groep.

Hoofdstuk 6. Ziekte van Hirschsprung bij kinderen met het syndroom van Down: een vergelijkende studie.
Onder de 149 kinderen, die in de periode 1987 - 2008 in het Wilhelmina Kinderziekenhuis in Utrecht voor de ziekte van Hirschsprung zijn geopereerd waren er 20 die tevens het syndroom van Down hadden. Alle kinderen ondergingen een open of een laparoscopische Duhamel procedure. De postoperatieve complicaties en het resultaat van de groep patiënten met en zonder het syndroom van Down werden vergeleken. Postoperatieve naadlekkage kwam significant vaker voor bij kinderen met het syndroom van Down (n = 5, 25%) in vergelijking met normale kinderen (n = 1, 0,7%, p <0,0001). Postoperatieve lekkage-gerelateerde abcesvorming was hoger in de Down syndroom groep (n=3, 15% vs 0%). Binnen de syndroom van Down groep was er geen significant verschil tussen de open of laparoscopische Duhamel procedure met betrekking tot deze postoperatieve complicaties. Het postoperatief verblijf was significant langer voor kinderen met het syndroom van Down (p <0,05). In de syndroom van Down groep was er een iets korter verblijf in het ziekenhuis na laparoscopische Duhamel.
Ernstige constipatie kwam significant vaker voor bij kinderen met het syndroom van Down (55%) in vergelijking met kinderen zonder het syndroom van down (22,3%). Postoperatieve enterocolitis kwam vaker voor bij kinderen met het syndroom van Down. Er was geen verschil in incontinentie tussen de twee groepen.
Concluderend: kinderen met het syndroom van Down hebben een hoger percentage postoperatieve complicaties en een langer verblijf in het ziekenhuis. Tijdens de lange-termijn follow-up zijn de meeste patiënten met het syndroom van Down ernstiger geconstipeerd en hebben een hogere incidentie van enterocolitis.

Hoofdstuk 7. Is volledige resectie van de aganglionaire darm altijd nodig wanneer de aganglionosis tot in het midden van het ileum reikt?
Het totaal aganglionaire colon is een ongebruikelijke vorm van de ziekte van Hirschsprung. De incidentie varieert van 5% tot 15% van alle gevallen van de ziekte van Hirschsprung. Morbiditeit en mortaliteit zijn hoger dan bij de klassieke vorm van de ziekte van Hirschsprung. Van 163 kinderen met de ziekte van Hirschsprung behandeld in het Wilhelmina Kinderziekenhuis te Utrecht over een periode van 22 jaar zijn er 15 gevallen geopereerd met een totaal aganglionair colon. De uitkomst van deze kinderen werd geanalyseerd met betrekking tot postoperatieve complicaties, sterfte en follow-up. Bij drie speciale gevallen, waarbij de aganglionosis tot in het midden van het ileum reikte werd aganglionair ileum in situ gelaten om "het korte darmsyndroom" en de complicaties ervan te voorkomen. Het uiteindelijk resultaat bij deze kinderen was bevredigend. Deze behandelingsmogelijkheid van aganglionose reikend tot halverwege het ileum is niet eerder beschreven. Resultaten: De incidentie van enterocolitis is bij totale colon aganglionosis hoger (46%) dan bij de klassieke vorm (21,8%). Perianale dermatitis, één van de meest voorkomende complicaties na de pull-through operatie, heeft de neiging met de tijd af te nemen. Twaalf van de 15 patiënten presenteerden zich tijdelijk met perianale dermatitis. In onze reeks hadden we een uitzonderlijk geval waarin het probleem niet beheersbaar was. Vier jaar na de pull through operatie kreeg de patiënt een ileostoma. Het sterftecijfer is relatief hoog in vergelijking met de klassieke vorm van de ziekte van Hirschsprung. We hebben een review gepubliceerd van 55 gevallen van de klassieke ziekte van Hirschsprung met een sterfte van 0%. Het sterftecijfer in deze serie van totale colon aganglionosis bedraagt 13,3% Bij proximale uitbreiding van de aganglionosis tot in de dunne darm is het terminale ileum in ongeveer 75% van de gevallen betroffen, het midden van de ileum in 20%, en het jejunum in 5%. In onze drie gevallen met midileum betrokkenheid, hebben we besloten niet verder te gaan met de resectie dan het niveau van het ileostoma, dat goed bleek te functioneren, teneinde de korte darm complicaties in verband met een uitgebreidere darmresectie te vermijden. Eén patiënt overleed aan onbekende oorzaak, waarbij kan worden gespeculeerd of dit is veroorzaakt door aangeboren centrale hypoventilatie syndroom waarvan bekend is dat dit verband kan houden met de ziekte van Hirschsprung. Met de overige twee patiënten gaat het goed, zij hebben een regelmatige stoelgang. De incidentie van enterocolitis leek niet hoger te zijn dan bij

andere gevallen van totaal aganglionair colon omdat slechts één patiënt een episode had van enterocolitis. De twee patiënten hadden geen lange termijn parenterale voeding nodig en hebben geen perianale excoriaties op lange-termijn follow-up.
Concluderend: totaal aganglionair colon is een bijzondere vorm van de ziekte van Hirschsprung, die vaak gepaard gaat met een verhoogde morbiditeit en mortaliteit. Resectie van aganglionaire darm is aangewezen om obstructie en haar gevolgen, zoals enterocolitis, te verlichten. Er komt echter een moment waarop de balans kan kantelen en de complicaties van het korte darm syndroom zich negatief verhouden tegen het voordeel van volledige resectie. In gevallen met een goed functionerend ileostoma in aganglionair gebied, kan het in situ laten van de resterende aganglionaire darm van voordeel zijn. De behandeling van patiënten met aganglionose tot in de dunne darm behoeft nog verder onderzoek en follow-up.

Discussie: Vele verschillende aspecten kunnen worden betrokken bij de oorzaken van de aanhoudende motiliteits- en ontlastingproblemen na de chirurgische behandeling voor de ziekte van Hirschsprung, zoals de aanwezigheid van geassocieerde neuronale intestinale misvorming in de verwijderde en de resterende darm. We konden een verband aantonen tussen de histologische bevindingen in het proximale resectievlak en de postoperatieve uitkomst. Patiënten met aganglionose en hypoganglionose in het proximale resterende deel van de darm hebben meer kans op problemen bij de ontlasting dan patiënten met een normale histologie. Patiënten met intestinale neuronale dysplasie (NID B) hebben iets meer risico op constipatie die de neiging heeft te verbeteren tot de leeftijd van 4 jaar. We hebben ook opgemerkt dat bij meer uitgebreide resectie van het colon de histologische bevindingen van het proximale segment minder belangrijk zijn met betrekking tot de postoperatieve uitkomst. De criteria voor de diagnose van NID B zijn onlangs gewijzigd: de diagnose moet worden bepaald na de leeftijd van 1 jaar, want eerder in het leven kunnen gigantische ganglia voorkomen bij asymptomatische patiënten. Hiermee lijkt het belang van NID B bij de behandeling van patiënten met de ziekte van Hirschsprung te zijn afgenomen.
Als specifiek naar subgroepen wordt gekeken kan gesteld worden, dat de patiënten met het syndroom van Down en de ziekte van Hirschsprung meer kans hebben om postoperatieve complicaties te krijgen zoals anastomose lekkage en abcesvorming dan de kinderen met geïsoleerde

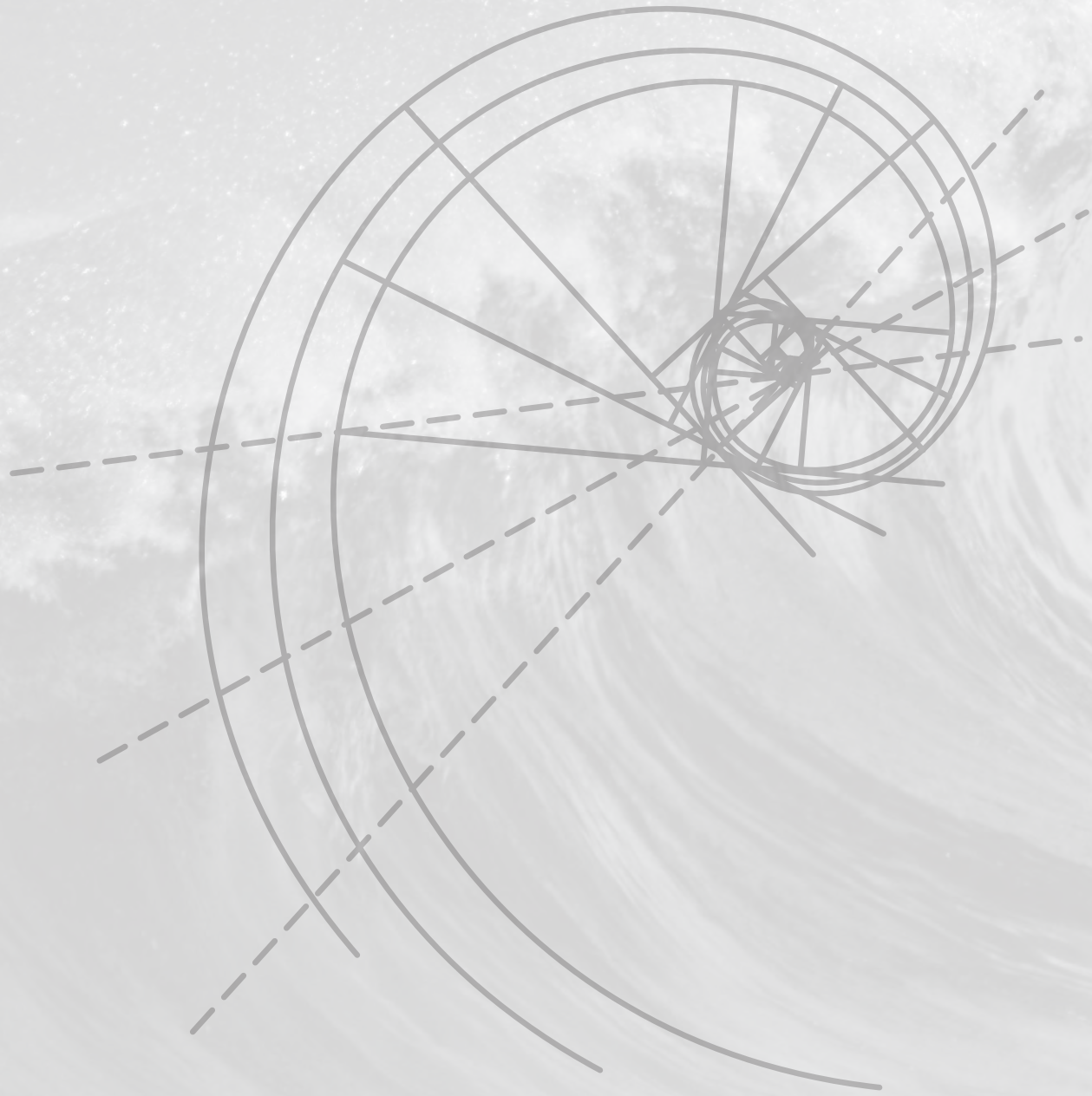
ziekte van Hirschsprung. Bovendien is er een hogere incidentie van constipatie dan bij de andere kinderen met de ziekte van Hirschsprung. Totale aganglionosis van het colon is ook een aparte groep van de ziekte van Hirschsprung. Deze groep heeft de neiging tot een hogere morbiditeit en mortaliteit dan kinderen met klassieke vorm van Hirschsprung en toont meer problemen zoals diarree, perineale ontvelling en korte darm sydroom. Gevallen van aganglionose tot het midden van het ileum komen niet vaak genoeg voor (20% van alle patiënten met totale aganglionose) om een ruime ervaring in één afdeling te krijgen. In drie gevallen van uitgebreide aganglionose tot op het midden van het ileum, waarbij het ileostoma dat in aganglionair gebied lag maar goed functioneerde, hebben we niet de volledige aganglionaire dunne darm verwijderd om "korte darm syndroom" complicaties te voorkomen. Het in situ laten van aganglionaire darm, als het aganglionair ileostoma goed functioneert, is een nieuw alternatief in de behandeling van uitgebreide totaal aganglionosis dat verdere studie vereist.

Laparoscopische versus open procedure: Er is geen significant verschil tussen de open en laparoscopische Duhamel procedure met betrekking tot de postoperatieve uitkomst, behalve voor een korter verblijf in het ziekenhuis, een kortere tijd tot de eerste orale voeding en een lagere incidentie van adhesieve obstructie in het voordeel van de laparoscopische procedure. Onze bevinding dat er geen grote verschillen zijn tussen de open en de laparoscopische techniek wordt ook door andere auteurs ondersteund. De cosmetiek is in onze studie niet onderzocht, maar lijkt wel evident in het voordeel van de laparoscopische benadering uit te vallen.

Conclusie: Verschillende aspecten met betrekking tot de postoperatieve uitkomst van de ziekte van Hirschsprung zijn besproken in dit proefschrift. Het mysterie waarom een bevredigend resultaat niet altijd kan worden bereikt, is nog niet volledig opgelost. We hebben geleerd, dat het proximale resectiepreparaat ons iets kan zeggen over het functionele resultaat van de ziekte van Hirschsprung en en dat de rol van NID B beperkt is. NID B heeft zelfs alleen een invloed bij kinderen ouder dan een jaar. De laparoscopische benadering heeft geen negatieve effecten op de uitkomst van chirurgie en de cosmetiek zal waarschijnlijk in de toekomst een beslissende rol gaan spelen in het voordeel van de laparoscopie.

Speciale subgroepen, zoals kinderen met Down syndroom of totaal aganglionair colon hebben onze speciale aandacht nodig, en concentratie in gespecialiseerde centra is wenselijk. Kinderen bij wie de ziekte

van Hirschsprung zich uitbreidt tot in de dunne darm, zouden een voordeel kunnen hebben, om, wanneer het aganglionaire ileostoma goed functioneert, het resterende aganglionaire deel proximaal van het stoma in situ te laten. Dit zou de problemen van “korte darm syndroom” kunnen voorkomen.
Tot op heden is de ziekte van Hirschsprung nog steeds een niet te genezen complexe entiteit gebleken, waar nog veel van te leren en te onderzoeken valt om zodoende de best mogelijke resultaten voor onze patienten te bereiken.



Deutsche Zusammenfassung

Einleitung:
Morbus Hirschsprung ist ein faszinierendes und gleichermaßen wichtiges Thema in der Kinderchirurgie.
Es handelt sich um eine der Hauptursachen des Ileus und der Obstipation bei Neugeborenen und Kleinkindern.
Histologisch definiert wird das Bild durch die Abwesenheit von Ganglienzellen in der Darmwand. Diese fehlen im internen analen Sphinkter und in variabler Ausdehnung nach proximal hin im Dickdarm- und manchmal auch im Dünndarmbereich. Der Defekt entsteht während der Embryogenese durch eine Unterbrechung der Migration der Ganglienzellen aus der Neuralleiste.
Die klassische Aganglionose ist in 80 % der Fälle auf das Rectosigmoid beschränkt. Ein sogenanntes `langes Segment´ existiert in 11% bis 26%, die totale Aganglionose tritt in 5 bis 15% aller Fälle auf.
Morbus Hirschsprung ist nicht heilbar. Alle üblichen operativen Verfahren lassen ein kurzes aganglionäres Segment zurück.
Die chirurgische Behandlung des Morbus Hirschsprung vermindert das Auftreten von Komplikationen und verbessert Morbidität und Mortalität. Sie kann jedoch nicht die Grundursache beheben, das Fehlen der Neuronen des enterischen Nervensystems.
Daher sind postoperativ auftretende Darmmotilitäts-Störungen trotz einer operativen Behandlung häufig. Im Einzelnen sind dies die chronische Obstipation, Überlaufenkopresis, Inkontinenz und Enterokolitis.
Die vorliegende Arbeit analysiert die verschiedenen Aspekte der möglichen Ursachen dieser komplexen Störungen vor und nach der chirurgischen Behandlung des Morbus Hirschsprung.

Kapitel 2. Klinische Auswirkungen intestinaler neuronaler Fehlbildungen: Ergebnisse einer prospektive Studie an 141 Patienten
141 Patienten mit diagnostizierten neuronalen intestinalen Fehlbildungen wurden analysiert. Unter diesen fanden sich die Aganglionose, die neuronale intestinale Dysplasie (NID B), die Hypoganglionose, die Unreife der Ganglienzellen, der verminderte Parasympathikotonus, die Heterotopie des submukösen Plexus, die Heterotopie des Plexus myentericus und die milde Dysganglionose.
Hauptsymptome waren Obstipation bei 83 (58,9%) und Ileus bei 43 (30,5 %) der Patienten. Die Kombination aus Aganglionose und NID B präsentierte sich präoperativ häufiger (73,5%) durch ein Ileusbild als die isolierte Aganglionose (32,5%).

Eine Darmresektion war bei allen Patienten mit Aganglionose und bei sieben von neun Kindern mit Hypoganglionose erforderlich. Nachresektionen mussten bei sieben Kindern mit Aganglionose vorgenommen werden (9,6%). Von diesen Kindern hatten sechs eine assoziierte NID B und ein Kind eine isolierte Aganglionose. Unter den Patienten mit reiner NID B benötigte lediglich einer eine Resektion mit anschließender Nachresektion. Zwei weitere Patienten dieser Gruppe konnten ausschließlich durch eine temporäre Kolostomie ohne Resektion behandelt werden.
Bei der Nachuntersuchungskontrolle nach 2,4 (± 1,4) Jahren hatten 69% der an isolierter Aganglionose operierten Kinder eine normale Darmtätigkeit. Dabei bestand kein signifikanter Unterschied zwischen den Fällen reiner Aganglionose und den mit NID B assoziierten Fällen.
Von den 66 Patienten ohne Aganglionose waren bei der Nachuntersuchungskontrolle insgesamt 29 (43,9%) asymptomatisch. In der Untergruppe von 12 Patienten, die wegen Hypoganglionose und übriger neuronaler intestinaler Fehlbildungen reseziert wurden, hatten lediglich vier eine normale Darmtätigkeit (33%). Dies entspricht der häufig schlechteren postoperativen Prognose bei Patienten mit Hypoganglionose. Daraus wird geschlossen, dass nicht nur die typische Aganglionose sondern auch einige andere neuronale intestinale Fehlbildungen eine relevante klinische Bedeutung haben. Inzwischen haben uns neue Erkenntnisse gezeigt, dass NID B eigentlich erst nach dem ersten Lebensjahr von Bedeutung ist, wohingegen die Kinder mit Morbus Hirschsprung schon vor dem ersten Lebensjahr symptomatisch sind.

Kapitel 3. Bestimmung der intestinalen Transitzeit bei Kindern mit neuronalen intestinalen Fehlbildungen und die Symptomen eines Morbus Hirschsprung

Transitzeit-Studien wurden dazu bei 106 Patienten mit unterschiedlichen Typen neuronal intestinaler Fehlbildungen durchgeführt. Im Ergebnis waren die Transitzeiten bei allen 53 Kindern mit Aganglionose und bei 37 der übrigen 53 Kinder (69,8%) mit anderen neuronalen intestinalen Fehlbildungen verlängert. Dabei wurden abnormale Transitzeiten in 50% der NID B Fälle gefunden, in 87,5% der Hypoganglionose-Patienten, in 90% der Kinder mit vermindertem Parasympathikotonus und bei beiden Kindern mit Heterotopie des Plexus myentericus. Von den verbleibenden übrigen neuronalen intestinalen Anomalien hatten 7 von 11 eine verlängerte Transitzeit.

Alle Kinder mit Aganglionose und alle Hypoganglionose-Fälle mit verzögerter Darmpassage wurden operiert. Keines der Kinder mit normaler Transitzeit hatte eine Resektion nötig.
Die Bestimmung der intestinalen Transitzeit ist deshalb eine wichtige Methode zur Erfassung der klinischen Relevanz pathohistologischer Befunde.

Kapitel 4. Die postoperative Darmfunktion beim Morbus Hirschsprung kann anhand der Histologie des proximalen Segmentes am resezierten Darm vorhergesagt werden.
101 Patienten mit Morbus Hirschsprung wurden an der Kinderklinik der Stadt Köln im Verfahren nach Rehbein operiert. Deren histologische Befunde am resezierten proximalen Segment wurden mit der postoperativen Darmfunktion verglichen. Im Ergebnis korrelierte ein histologisch unauffälliges proximales Darmsegment mit einer guten postoperativen Darmfunktion, die Konstipationsrate betrug 10,5%.
Bei neuronaler intestinaler Dysplasie am proximalen Segment wurde eine etwas höhere Konstipationsrate von 17,8% gefunden. Etwas deutlicher beeinträchtigt war die postoperative Darmfunktion bei der Hypoganglionose mit einer Konstipationsrate von 23,1%. Alle 4 Patienten mit Aganglionose des proximalen Segmentes verzeichneten hingegen erhebliche postoperative Probleme: zwei erforderten eine Nachresektion, einer hatte wiederkehrende Episoden von Enterokolitis und ein Patient verstarb.
Eine allgemeine Beobachtung dieser Studie war, dass die histologische Klassifizierung des proximalen Segmentes an Bedeutung verlor, wenn es sich um eine umfangreiche Kolonresektion handelte. War eine über die Links-Hemikolektomie hinausgehende Darmresektion durchgeführt worden, konnte in 72,1% der Fälle eine normale Darmfunktion beobachtet werden, obwohl nur ein Drittel von diesen Patienten (32,3%) eine normale Histologie am proximalen Segment aufwies.

Zusammenfassend besteht eine deutliche Korrelation zwischen dem histologischen Befund am resezierten proximalen Segment und der postoperativen Darmfunktion. Bei Resektionen über die Links-Hemikolektomie hinaus verliert diese Korrelation etwas an Bedeutung.

Kapitel 5. Das Operationsverfahren nach Duhamel in offener versus laparoskopischer Technik: Eine vergleichende retrospektive Studie

Am Wilhelmina Kinderkrankenhaus in Utrecht wurde eine vergleichende Studie durchgeführt zwischen Patienten mit offenem Duhamel Verfahren (N = 25) und laparoskopischem Duhamel Verfahren (N = 30). Um Homogenität zwischen den beiden Gruppen zu erreichen wurden Patienten mit ausgedehnter Aganglionose, des Weiteren solche mit präoperativ angelegtem Kolostoma und diejenigen mit einem Syndrom ausgeschlossen. Endpunkte waren intraoperative Komplikationen, postoperative Komplikationen, Zeit bis zur ersten Nahrungsaufnahme, Dauer des Krankenhausaufenthalts und das Ergebnis im Follow-up.
Es gab keine intraoperativen Komplikationen in beiden Gruppen. Es wurden keine signifikanten Unterschiede im Follow-up beobachtet. Allerdings gab es eine in der Tendenz höhere Enterokolitisrate in der laparoskopischen Gruppe. Es gab keinen Bridenileus in der laparoskopischen Gruppe im Gegensatz zu drei Fällen in der offenen Gruppe. Stuhlinkontinenz kam in beide Gruppen nicht vor. Abgesehen von einem kürzeren Krankenhausaufenthalt und einer kürzeren Zeit bis zur ersten Nahrungsaufnahme in der laparoskopisch operierten Gruppe, konnten auf diese Weise zusammenfassend keine signifikanten Unterschiede beobachtet werden. Das kosmetische Ergebnis war kein Endpunkt, aber zweifelsohne besser in der laparoskopischen Gruppe.

Kapitel 6. Morbus Hirschsprung bei Kindern mit Down-Syndrom: Eine vergleichende Studie

Von 149 Kindern, die zwischen 1987 und 2008 am Wihelmina Kinderkrankenhaus in Utrecht am Morbus Hischsprung operiert wurden, litten 20 zusätzlich an einem Down-Syndrom. Alle Kinder wurden nach Duhamel operiert, entweder im offenen oder im laparoskopischen Verfahren. Die postoperativen Komplikationen und die Nachuntersuchungsergebnisse der zwei Gruppen wurden verglichen. Eine postoperative Anastomoseninsuffizienz trat signifikant häufiger bei Kindern mit Down-Syndrom auf (N = 5, 25%) im Vergleich zu Kindern ohne Down-Syndrom (N = 1, 0,7%, p <0,0001). Die postoperative Abszessbildung im Zusammenhang mit einer Anastomoseinsuffizienz war in der Down-Syndrom-Gruppe im Vergleich höher (n = 3, 15% versus 0%). Innerhalb der Down-Syndrom-Gruppe gab es keinen signifikanten Unterschied hinsichtlich offener oder laparoskopischer Technik betreffend diese postoperativen Komplikationen.

Der postoperative Krankenhausaufenthalt war signifikant länger in der Down-Syndrom-Gruppe im Vergleich zu den Kindern ohne Down-Syndrom ($p < 0,05$). Wurden die Down-Syndrom Kinder laparoskopisch operiert, so war ihr Krankenhausaufenthalt etwas kürzer als nach einer offenen Duhamel Operation.
Schwere Obstipation war signifikant häufiger bei den Kindern mit Down-Syndrom (55%) als in der Gruppe ohne Down-Syndrom (22,3%). Eine postoperative Enterokolitis trat häufiger auf bei den Kindern mit Down-Syndrom. Es gab keinen Unterschied bezüglich Inkontinenz zwischen den beiden Gruppen.
Zusammenfassend haben Kinder mit Down-Syndrom eine höhere Inzidenz an postoperativen Komplikationen und einen längeren Krankenhausaufenthalt. Im langfristigen Follow-up sind die meisten Patienten mit Down-Syndrom stark obstipiert und haben eine höhere Inzidenz der Enterokolitis.

Kapitel 7. Ist eine vollständige Resektion des aganglionären Darmes bei ausgedehnter totaler Aganglionose ab mittlerem Ileum immer notwendig?

Totale Aganglionose ist eine ungewöhnliche Form des Morbus Hirsch–sprung mit einer Inzidenz von 5% bis 15% aller Fälle. Die Morbidität und Mortalität in dieser Patientengruppe ist bekanntermaßen höher als bei der klassischen Form des Morbus Hirschsprung.
In einem Zeitraum von 22 Jahren wurden am Wihelmina Kinder–krankenhaus in Utrecht 163 Kinder mit Morbus Hirschsprung operiert. Dabei lag in 15 Fällen eine totale Aganglionose vor.
In einer retrospektiven Studie wurden die Ergebnisse dieser Fälle analysiert hinsichtlich postoperativer Komplikationen, Mortalität und Follow-up. Bei drei besonderen Fällen mit ausgedehnten totalen Aganglionose bis zum mittlerem Ileum wurde aganglionärer Darm in situ belassen, um ein Kurzdarmsyndrom und dessen Komplikationen zu vermeiden. Die Ergebnisse waren zufriedenstellend. Diese Form der Behandlung bei ausgeprägter totaler Aganglionose ist bisher nicht beschrieben.
Im Detail ergaben sich folgende Ergebnisse: die Inzidenz der Entero–kolitis war bei totaler Aganglionose höher als beim klassischen Morbus Hischsprung. Wir hatten eine Enterokolitis-Inzidenz von 46%, damit deutlich höher verglichen mit der von uns früher veröffentlichten Inzidenz von 21,8% beim klassischen Morbus Hirschsprung.

Perineale Dermatitis ist eine der häufigsten Komplikationen nach Durch–zugsoperationen. Ihre Häufigkeit nimmt im Laufe der Zeit ab. In unserem Kollektiv präsentierten 12 der 15 Patienten eine temporäre perineale Dermatitis. Bei einem der Patienten war das Problem dergestalt gravierend, dass noch 4 Jahre postoperativ ein Ileostoma angelegt werden musste.
Die Sterblichkeit der totalen Aganglionose ist bekannterweise relativ hoch im Vergleich zur klassischen Form des Morbus Hirschsprung. In unserer Serie lag die Sterblichkeitsrate in den Fällen totaler Aganglionose bei 13,3%, verglichen mit einer von uns in der Vergangenheit publizierten Mortalität von 0% bei 55 Fällen des klassischen Morbus Hirschsprung.
Bei unseren drei Fällen der ausgedehnten totalen Aganglionose handelte es sich um eine Pathologie bis hinauf in das mittlere Ileum. Zur Einordnung dieser ausgedehnten Erkrankung wird in der Literatur eine proximale Ausdehnung der totalen Aganglionose bis in das terminale Ileum in etwa 75% der Fälle angegeben, bis in das mittlere Ileum – wie in unserem Fällen - in 20%, und bis zum Jejunum in den verbleibenden 5%. Um das Kurzdarmsyndrom nach erweiterter Darmresektion zu vermeiden, entschieden wir uns bei funktionstüchtigem Ileostoma nicht höher zu resezieren als bis zu diesem Niveau. Von unseren drei solchen Fällen entwickelten sich zwei Patienten zufriedenstellend und mit normalem Stuhlgang. Ein Patient verstarb an unklarer Ursache, mutmaßlich aufgrund einer angeborenen zentralen Hypoventilation, die bekanntermaßen im Zusammenhang mit Morbus Hirschsprung auftreten kann.
Die Inzidenz der Enterokolitis schien hier nicht höher zu sein als in den übrigen Fällen totaler Aganglionose, da nur ein Patient eine einzige Episode Enterokolitis hatte. Alle Patienten brauchten postoperativ keine langfristige parenterale Ernährung und perineale Dermatitis trat nicht auf.
Zusammenfassend ist die totale Aganglionose eine besondere Form des Morbus Hirschsprung, die mit einer erhöhten Morbidität und Mortalität einhergeht. Die Resektion des aganglionären Darms ist zwingend notwendig, damit Obstruktion und deren Folgeerscheinungen wie Enterocolitis vermieden werden. Dies gilt ebenfalls für eine totale Aganglionose bis in das terminale Ileum. In den seltenen Fällen einer noch weitergehenden totalen Aganglionose hingegen - wie hier ab mittlerem Ileum - halten wir ein kritisches Abwägen für geboten zwischen dem Nutzen einer ausgedehnten Dünndarmresektion gegen die Komplikationen eines drohenden Kurzdarmsyndroms. Hier scheint die Waage zu kippen,

und die Komplikationen des Kurzdarmsyndroms beginnen den Nutzen der Resektion zu überwiegen. Daher kann in diesen Fällen das Belassen eines aganglionären Dünndarmsegmentes bei gut funktionierendem Ileostoma eine vorteilhafte Option darstellen. Insgesamt verdient die Behandlung von Patienten mit ausgedehnter totaler Aganglionose ein großes Augenmerk und weitergehende Untersuchungen.

Diskussion: Viele verschiedene Aspekte können als Ursache anhaltender Motilitäts- und Defäkationsstörungen nach chirurgischer Behandlung des Morbus Hirschsprung in Frage kommen. Das Vorhandensein von assoziierten neuronalen intestinalen Fehlbildungen im zurückbleibenden Darm kann hierfür ein Grund sein. Der histologische Befund des proximalen Segmentes am resezierten Darm lässt eine gute Voraussage des postoperativen Ergebnisses zu. Patienten mit Aganglionose und Hypoganglionose am proximalen Segment tragen ein höheres Risiko postoperativer Obstipation und anderer Stuhlgangsprobleme als solche mit normaler Histologie. Patienten mit neuronaler intestinalen Dysplasie (NID B) des proximalen Segmentes haben postoperativ ein leicht erhöhtes Obstipationsrisiko, welches bis zum Alter von vier Jahren zur Verbesserung neigt. Bei allen Resektionen über die Links-Hemikolektomie hinaus verliert die Korrelation des histologischen Befunds am proximalen Segment mit dem postoperativen Ergebnis etwas an Bedeutung.
Die Kriterien für die Diagnose einer NID B haben sich vor kurzem geändert: die Diagnose soll erst nach dem ersten Lebensjahr gestellt werden, weil auch bei asymptomatischen Patienten in der frühen Lebensphase submuköse Riesenganglien auftreten können. Dies würde - retrospektiv betrachtet - das von uns ursprünglich ermittelte Vorkommen der NID B vermindern.
Bei Patienten mit der Kombination aus Down-Syndrom und Morbus Hirschsprung ist das Risiko postoperativer Komplikationen wie Nahtinsuffizienz und Abszessbildung deutlich erhöht im Vergleich zu Kindern mit einem isolierten Morbus Hirschsprung. Darüber hinaus leiden sie postoperativ häufiger an Obstipation.
Die totale Aganglionose ist eine andere distinkte Gruppe. Morbidität und Mortalität sind höher als beim klassischen Morbus Hirschsprung. Oft bestehen im Zusammenhang mit ausgedehnten Darmresektionen Probleme wie Durchfall, perineale Dermatitis und Kurzdarmsyndrom. Die komplexen Fälle einer totalen Aganglionose über das terminale Ileum

hinaus betragen 20% aller totalen Aganglionosen und sind somit so selten, dass eine grosse Erfahrung an einem einzelnem Zentrum nicht erlangt werden kann. In den beschriebenen drei Fällen einer totalen Aganglionose bis hinauf in das mittlere Ileum, in denen das Ileostoma gut funktioniert hat, beließen wir ein Segment aganglionären Dünndarms in situ, um die Komplikationen des Kurzdarmsyndroms zu vermeiden. Hiermit präsentieren wir eine neue Alternative in der Behandlung dieser Formen der ausgedehnten totalen Aganglionose, zu der weitere Studien sinnvoll erscheinen.
Laparoskopisches versus offenes Verfahren: Es gibt keine wesentlichen Unterschiede beider Verfahren in der Operation nach Duhamel hinsichtlich des postoperativen funktionellen Ergebnisses. Krankenhausaufenthalt und Zeit bis zur ersten oralen Nahrungsaufnahme sind kürzer beim laparoskopischen Vorgehen, ebenso ist die Inzidenz des Bridenileus geringer. Diese Beobachtungen werden unterstützt von anderen Autoren, die ebenfalls keine wesentlichen Unterschiede beider Vorgehensweisen fanden, unabhängig von der Wahl der Operation. Eine Ausnahme ist die Operation nach Georgeson, die Vorteile im laparoskopischen Verfahren bei der Kontinenzprognose sieht.

Abschluss: Viele grundlegende Aspekte und neue Entwicklungen zum postoperativen Ergebniss beim Morbus Hirschsprung sind in dieser Arbeit diskutiert worden. Nichtsdestoweniger bleibt es ein Mysterium, warum in manchen Fällen trotz operativer Therapie kein zufrieden stellendes Ergebnis erreicht werden kann.
Wir haben gelernt, dass die histologische Beurteilung des proximalen Segments die postoperative Darmfunktion vorhersagen kann und dass die NID B jenseits des ersten Lebensjahres bezüglich des funktionellen Ergebnisses nur eine kleine Rolle spielt.
Das laparoskopische Verfahren hat keine Nachteile und die kosmetischen Ergebnisse werden in Zukunft eine Schlüsselrolle zu Gunsten der Laparoskopie einnehmen.
Besondere Gruppen wie Patienten mit Down-Syndrom oder Patienten mit totaler Aganglionose benötigen mehr Aufmerksamkeit. Ihre Behandlung in wenigen spezialisierten Zentren ist wünschenswert, um ein optimales Ergebnis für diese Patientengruppen zu erreichen. Patienten mit der seltenen Extremform einer bis zum Ileum ausgedehnten Aganglionose können in Zukunft vom Belassen eines aganglionären Dünndarmsegmentes profitieren unter der Voraussetzung eines gut

funktionierenden Ileostoma, um ein Kurzdarmsyndrom zu vermeiden.
Zusammenfasssend ist der Morbus Hirschsprung eine nicht heilbare komplexe Erkrankung, bei der noch viel zu lernen und zu erforschen bleibt, um die bestmöglichen Ergebnisse für unsere Patienten zu erreichen.

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"Neither fire nor wind,

birth nor death

can erase your good deeds."
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Curriculum Vitae

Daisy Vieira Travassos was born on June 18th 1965 in Patrocinio, Brazil. She attended medical school at the Faculdade de Ciencias Medicas, Belo Horizonte, Brazil from which she graduated in 1989. Her training in general surgery took place at Heliopolis Hospital in São Paulo, Brazil from 1990 to 1991. Heliopolis Hospital is one of the largest public hospitals in the region of São Paulo city serving the most disadvantage segment of the population there. Her subsequent training in pediatric surgery was undertaken at Unicamp (Campinas University Hospital) from 1992 to 1994.

In 1994 she was awarded a scholarship by the German government (DAAD- Deutscher Akademischer Austausch Dienst) to do research on Hirschsprung's disease and allied disorders at the Children's Hospital of the city of Cologne with Prof. Ure, under the supervision of Prof. Holschneider. In 2000 she received her German board certification for pediatric surgery.

In 2001 she moved to the Netherlands, as a staff member of the department of pediatric surgery at the Wihelmina Children's Hospital of the University of Utrecht where she has had the opportunity to gain experience in laparoscopic surgery with Prof. Klaas Bax and Prof. David van der Zee. Here she continued her studies in Hirschsprung's disease which resulted in this thesis.

She has two sons, Johann (1999) and Matthias (2005).