Hirschsprung's disease: early diagnosis and long-term outcomes

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CHAPTER 1

General introduction and aims

Hirschsprung's disease (HD) is a congenital defect of the intestines and is named after its discoverer, Harald Hirschsprung. Hirschsprung's report dates from 1887 and describes the medical cases of two infants who had died from constipation in association with extreme dilatation and hypertrophy of the colon.[1] At the time, Hirschsprung mistakenly believed that it was the dilated segment of the colon that was pathological. In 1949, more than half a century later, Swenson and colleagues came to the conclusion that not the dilated part of the colon was pathological, but the more distal, narrow part of the colon (Figure 1).[2] They reasoned that the extreme dilatation of the colon was caused by an inborn obstruction at the distal end of the intestines that was blocking the passage of feces. Backed by this theory, Swenson and Bill proceeded to remove the obstructing segment of the intestines and achieved surprisingly good results.[3] At around the same time as Swenson and colleagues were undertaking their surgical experiments, the underlying cause of HD was discovered by Whitehouse and Kernohan by comparing colon specimens of HD patients with colon specimens of non-HD controls.[4] In the former, they discovered a complete absence of ganglion cells in both plexuses of the enteric nervous system, as well as a profound hypertrophy of nerve bundles. These two discoveries revolutionized the diagnosis and treatment of HD and greatly improved the morbidity and mortality of patients who suffer from this previously fatal disease. Shortly after Swenson and Bill reported on their surgical technique, other techniques were developed, including those of Rehbein, Duhamel, and Soave.[5–7]

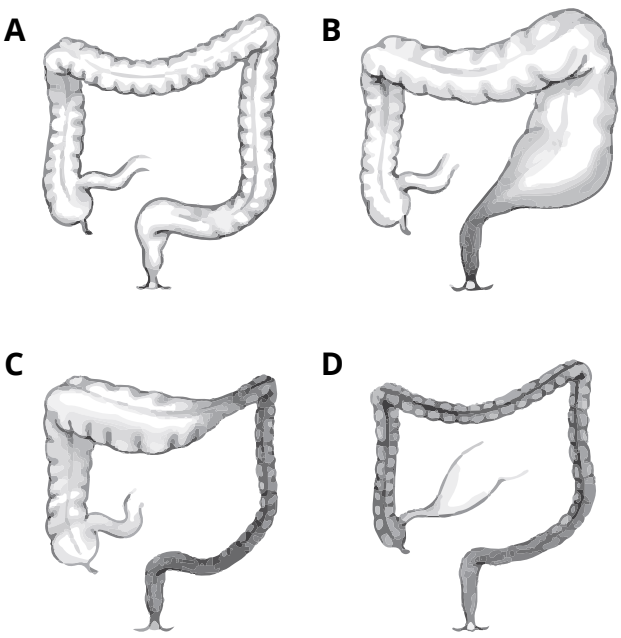

Figure 1
Different types of Hirschsprung's disease based on the length of the aganglionic intestines.
A: Normal bowel
B: Short-segment variant (up to the sigmoid)
C: Long-segment variant
D: Total colonic aganglionosis

Even today new discoveries are being made that help us to better understand the pathophysiology and improve the treatment of HD. An overview of these discoveries is given in this chapter, followed by the content and aims of this thesis.

ETIOLOGY

The main feature of HD is the absence of ganglion cells in the distal intestines. This was first discovered by Whitehouse and Kernohan in 1948.[4] The absence of ganglion cells, known as aganglionosis, is thought to be the result of faulty migration of neural crest cells during the embryonic development of the enteric nervous system.[8] In normal fetal development the neural crest cells migrate in a cranial-to-caudal direction between the 4th and 7th week of gestation, starting out from the esophagus and ending in the anal canal.[9] Currently, two theories exist that explain why these neural crest cells fail to reach the distal intestines. The first theory proposes that the cells mature or differentiate into ganglion cells too early during their migration.[10] The second theory proposes that they do reach their destination, but fail to differentiate, proliferate, or survive.[11,12] No hard evidence is available to confirm or refute either theory. The most likely explanation is that faulty migration is the result of a combination of factors, which can differ between individual patients.[13] In between the aganglionic and ganglionic intestines is a segment known as the transition zone. This zone contains a reduced number of ganglion cells and marks the transition between the healthy and HD-affected intestines. It is considered dysfunctional, similar to the aganglionic segment, because of its reduced number of ganglion cells and decreased peristalsis.

PATHOPHYSIOLOGY

In HD the affected intestines are characterized by a constant increased tonus of the smooth bowel muscles that blocks the passage of stool. In healthy intestines, smooth muscles cells are innervated by sympathic (inhibitory) neurons and parasympathic (excitatory) neurons. Jointly, these neurons are responsible for the motility of the gut in conjunction with the complex architecture of the enteric nervous system (Figure 2). The most important neurotransmitter responsible for inhibition is nitric oxide (NO). It mediates relaxation of smooth muscle cells along with other inhibitors, such as vasoactive intestinal polypeptide, and carbon monoxide.[14] Additionally, excitatory neurons produce neurotransmitters that mediate the contraction of smooth muscle cells, most importantly, acetylcholine (ACh).[14]

While HD is characterized by the absence of intrinsic ganglion cells in both plexuses, there are still nerve fibers that innervate the smooth muscle cells of the affected intestines (Figure 2). The exact origin of these nerve fibers is unknown. It is thought that they have an extrinsic origin, such as the pelvic nerve plexus, and proliferate into the bowel wall because of their failure to connect with the absent, intrinsic ganglion cells of the enteric nervous system.[15] For unknown reasons, the release by these nerve fibers of inhibitory neurotransmitters, such as NO, is decreased, while there is an increased release of excitatory neurotransmitters, such as ACh.[16,17] The increased excitation of the smooth muscle fibers by ACh and the absence of inhibition by NO, are thought to be responsible for the constant increased tonus of the intestines and the lack of propagation of peristaltic waves in HD.[18]

Another consequence of enteric nervous system abnormalities in patients with HD is the absence of the rectoanal inhibitory reflex.[19] In healthy bowels this reflex is responsible for the relaxation of the internal anal sphincter upon rectal distension and stimulation (Figure 3A). Relaxation of the internal anal sphincter is vital for the smooth passage of stool.

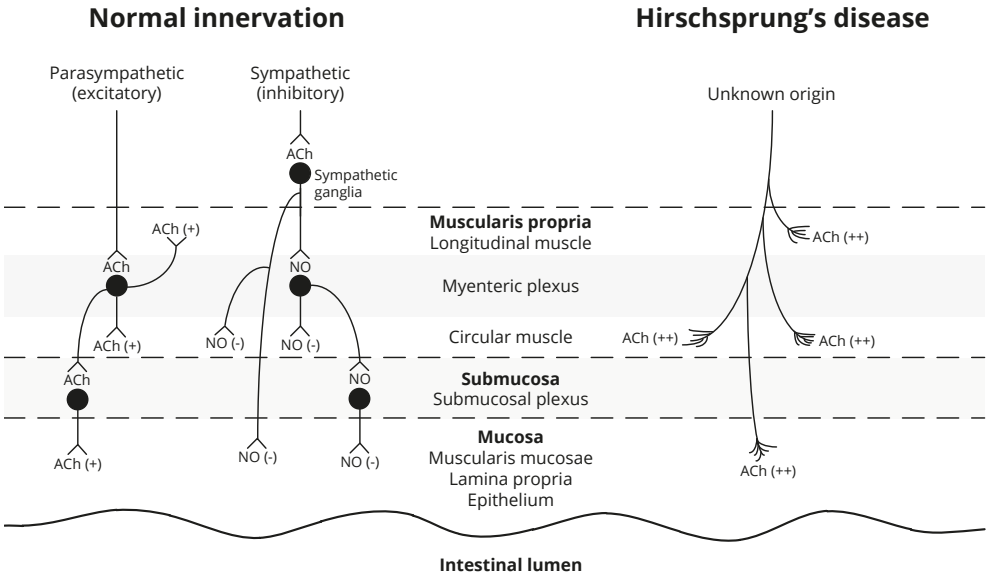

Figure 2

A schematic illustration of the layers of the intestinal wall with normal innervation (left) and innervation in case of Hirschsprung's disease (right). In normal innervation excitatory neurons and inhibitory neurons are balanced and coordinated by ganglion cells (●) of the enteric nervous system. In Hirschsprung's disease ganglion cells are absent in both plexuses, while a proliferation of extrinsic nerve fibers of unknown origin is present. The increased release of acetylcholine (ACh) by these fibers, in combination with the absence of inhibition by nitric oxide (NO), is thought to be responsible for the constant increased tonus of the intestines seen in Hirschsprung's disease.

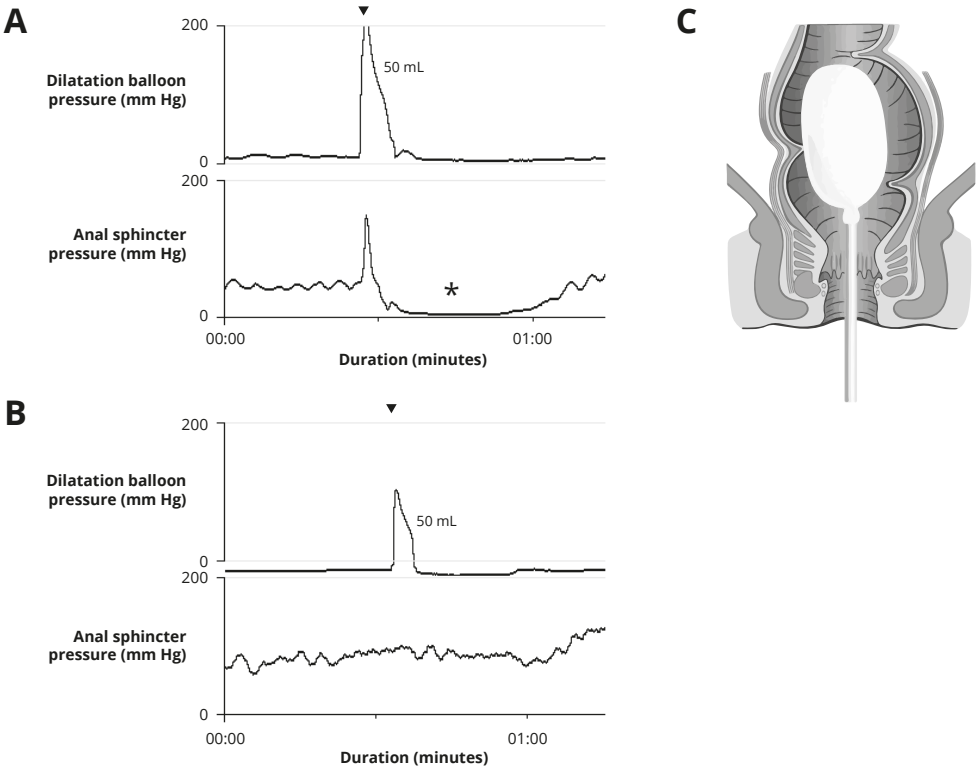

Figure 3

Anorectal manometry measurements.

A: Measurement in a healthy control showing a rectoanal inhibitory reflex (asterisk) following rectal dilatation (arrowhead).

B: Measurement in a patient with Hirschsprung's disease showing no response in anal sphincter pressure following rectal dilatation.

C: Illustration of the anorectal manometry catheter with a dilatation balloon at the tip of the catheter. The catheter is equipped with a pressure sensor at its tip to measure the dilation balloon pressure, as well as multiple pressure sensors at the level of the anal canal to measure changes in sphincter pressure.

Consequently, the absence of this reflex in HD contributes to the constipation complaints experienced by HD patients (Figure 3B). The absence of the rectoanal inhibitory reflex in HD was first reported by Schnaufer and collegues[20] and Lawson and Nixon[21] in 1967, and was later revealed to be caused by a lack of NO-producing inhibitory neurons.[22]

CLASSIFICATION

The classification of HD depends on the length of intestinal aganglionosis, which in turn depends on the developmental stage at which the migration of neural crest cells fails. If migration fails in an early stage of embryonic development, the aganglionic segment may be as long as the complete colon and part of the small intestines. If it fails at a later stage, the aganglionic segment may be limited to the anal canal and/or to the anal sphincter alone. The following types of HD are distinguished: the short-segment variant limited to the rectum and sigmoid (roughly 80% of the patients), the long-segment variant up to the splenic flexure or transverse colon (15%) and lastly, the total colonic variant (5%) (Figure 1).

In addition, there is a rare variant of HD, known as internal anal sphincter achalasia, previously ultrashort HD, in which aganglionosis is limited to the anal sphincter. This variant is characterized by normally innervated intestines but an absent rectoanal inhibitory reflex. Preferably this variant is treated conservatively with laxatives.[23] Lastly, the most extreme and rare variant of HD is total intestinal aganglionosis. Patients suffering from this type of HD have a very poor prognosis and the mortality rate is high.[24]

CLINICAL PRESENTATION

HD is a relatively rare cause of constipation and occurs in an estimated 1 to 2 cases per 10.000 live births.[25–27] Boys are affected more often than girls, especially in case of the shorter variant of HD in which the male-to-female ratio is 3:1.[25,28]

In the majority of the patients, HD presents shortly after birth with a failure to pass meconium during the first 24 to 48 hours. Nowadays, on account of this early presentation and overall increased awareness of the disease, HD is diagnosed in the neonatal period in 91% of the patients.[29] While a failure to pass meconium during the first 48 hours is not uncommon in otherwise healthy newborns, other symptoms such as a distended abdomen, feeding intolerance, and bilious vomiting often contribute to raising the suspicion of HD. Despite increasingly earlier diagnoses, still approximately 5% of patients with HD are diagnosed after the first year of life.[25] Especially patients with a shorter segment of aganglionosis, who suffer less severe symptoms of constipation,

are at higher risk of being diagnosed at a later age.[30] Patients in whom the disease has gone unnoticed present with symptoms such as chronic constipation with intermittent episodes of diarrhea, acute enterocolitis, or a sigmoid volvulus.[31–33]

Several other diagnoses may be associated with a delayed meconium passage and therefore mimic the symptoms of constipation seen in HD. Important diagnoses that should be considered in the differential diagnosis are: meconium ileus caused by cystic fibrosis, intestinal atresia, malrotation, anorectal malformation, and small left colon syndrome (associated with maternal diabetes). Additionally, several systemic disorders should be kept in mind as they could also be responsible for constipation, for example: electrolyte disorders, hypothyroidism, or constipation caused by maternal medication or drug use.

While most cases of HD seem to occur sporadically and isolated, it is estimated that 10% to 20% of the cases present with associated congenital anomalies, predominantly in the gastrointestinal tract, cardiovascular system, and urinary tract.[25,26,34] Chromosomal anomalies are also often seen in patients with HD. Especially the connection with Down syndrome seems significant, as Down syndrome accounts for 94% of all chromosomal anomalies in HD and has an incidence of 6% to 9% in the HD patient population.[25,26,34]

DIAGNOSTIC INVESTIGATIONS

While clinical presentation only suggests HD, the final diagnosis must be confirmed by the outcomes of rectal suction biopsy, anorectal manometry, and/or contrast enema. These three tests have been shown to have similar sensitivity and specificity, with the rectal suction biopsy considered to be the gold standard.[35,36]

Rectal suction biopsy

The rectal suction biopsy procedure entails extracting rectal tissue consisting of mucosal and submucosal material with a rectal suction biopsy tube. Generally, the procedure can be carried out without sedation or anesthesia. Rectal tissue is extracted at multiple levels above the anal verge and sent to a pathology laboratory for histologic examination. The tissue is examined for the presence of intrinsic ganglion cells and the proliferation of extrinsic nerve fibers. Absence of ganglion cells combined with proliferation of nerve fibers is compatible with HD. Rectal suction biopsies should be taken at least 2 cm from the edge of the pectinate line, as the first 1 to 2 cm physiologically have a reduced number of ganglion cells.[37] Furthermore, it is important to critically define the quality of the biopsy, as the extracted tissue should consist of sufficient submucosa for the appraisal of intrinsic ganglion cells.

Over the years various staining techniques have been introduced to analyze the tissue for intrinsic absence of ganglion cells and extrinsic proliferation of nerve fibers. The variety of staining options implies that no uniform approach to the analysis of rectal suction biopsies exists and, as a consequence, the approaches at different institutions vary. One approach is to only assess tissue on the presence of ganglion cells by staining with hematoxylin and eosin (H&E). Historically this proved effective but requires complete dedication and much time of the responsible pathologist, because many sections have to be inspected before a reliable diagnosis can be made. Another approach is to use more advanced staining techniques to make diagnosing quicker and easier. One of these staining techniques is acetylcholinesterase (AChE) histochemistry that was introduced by Meier-Ruge in 1972.[38] This technique can be used to judge the proliferation of extrinsic nerve fibers in HD that are typically rich in ACh and AChE (the enzyme which catalyzes the breakdown of ACh). AChE histochemistry increases the specificity of the rectal suction biopsy by reducing the number of false positive outcomes.[36] Despite making the diagnosis of HD quicker and easier, AChE histochemistry is generally considered to be a more sophisticated staining technique making it less suitable perhaps for institutions without high-end laboratory equipment. Besides, it has been shown that this attaining technique is difficult to interpret in neonates, which possibly leads to a higher false negative rate at these ages.[39,40] Therefore, newer staining techniques have been introduced, such as calretinin immunohistochemistry, which are believed to further increase the diagnostic accuracy of the rectal suction biopsy.[41] While there is increasing advocacy for calretinin immunohistochemistry,[42–44] a recent analysis pointed out that this technique might be associated with higher risks of false positive diagnoses, leading to unnecessary surgical intervention.[45] These new staining techniques might not completely replace AChE, but certainly constitute an important addition to the routine repertoire of stains used in the diagnosis of HD.

While the rectal suction biopsy is considered safe and reliable a small risk of complications, such as persistent rectal bleeding, remains.[46,47]

Anorectal manometry

Anorectal manometry can be used to examine anorectal physiology, including the presence of the rectoanal inhibitory reflex. As previously explained, absence of this reflex is a distinguishing feature of HD (Figure 3A).[19–21] The anorectal manometry procedure consists of inserting a catheter, equipped with pressure sensors and a small dilatation balloon at its tip, into the anal canal of the patient. The balloon is placed in the rectum and inflated slightly to simulate stool and to stimulate the rectal wall. As the rectal balloon is inflated the pressure sensors at the level of the anal canal should measure a decrease in

internal anal sphincter pressure, also known as the rectoanal inhibitory reflex (Figure 3B).

Several studies have demonstrated the value of anorectal manometry as a screening tool for HD, especially on account of its being non-invasive and having little to no risks.[48–51] It has been disputed, however, that it is generally more difficult to interpret in newborns, which in turn increases the risk of false negative and false positive test results.[36,48] As a consequence, few pediatric surgeons still use anorectal manometry for the purpose of diagnosing HD, while the majority opts for rectal suction biopsies as the diagnostic procedure of first choice.[52,53] Recent technological advances, however, such as the introduction of new catheters and high-resolution anorectal manometry, have increased diagnostic accuracy.[54] Anorectal manometry could therefore still be a valuable screening tool for HD, especially because it is non-invasive and its use could serve to reduce the number of invasive rectal suction biopsies.

Contrast enema

The last technique used in the diagnosis of HD is the contrast enema. This technique entails injecting a barium enema followed by an abdominal X-ray. A contrast enema carried out in a HD patient typically shows a contracted distal colon, a transition zone, and a distended colon in the caudal direction due to obstruction. Unfortunately, this characteristic image is not seen in all HD patients. For example, a contrast enema taken in a patient with a total colonic or an ultrashort variant of HD does not show the transition zone and the difference in intestinal caliber, which would lead to a false negative test result. The contrast enema has therefore lost its popularity as a diagnostic technique for HD, as its accuracy was shown to be inferior to anorectal manometry and rectal suction biopsy.[35,36] Accuracy also greatly depends on the expertise of the radiologist. For example, forceful injection of the contrast will distend the bowel and diminish accuracy of interpretation. It is therefore not uncommon to record a 24-hour delayed radiograph, which negates this effect. Indeed, Wong and colleagues found that a delayed radiograph can be useful to rule out HD.[55] Nevertheless, they suggested that it remains necessary to carry out a rectal suction biopsy to either exclude or confirm the diagnosis of HD. It therefore remains questionable whether the outcome of a 24-hour delayed radiograph following contrast enema actually has any clinical implications.

The contrast enema, despite its flaws as a diagnostic procedure, still remains the only investigation that can be used to evaluate the extent of aganglionosis and helps preoperative planning. A recent publication by Muller and colleagues, however, showed that the correlation of the radiographic transition zone with the level of aganglionosis remains low.[56] Their conclusion was that a biopsy remains mandatory to define the transition zone.

SURGICAL TREATMENT

A surgical reconstruction is usually performed to treat HD after the diagnosis is established. Reconstruction consists of removing the majority of the aganglionic intestines in order to restore bowel functionality. Nowadays, there are two major kinds of surgical strategies: the abdominal approach and the transanal approach.

The abdominal approach consists of surgical techniques such as the Swenson, Rehbein, Duhamel, and Soave procedures (Figure 4).[3,5–7] Most of these procedures have undergone alterations and modifications over the years, including the addition of laparoscopy.[57,58] In 1948, Swenson introduced a technique to resect aganglionic intestines.3 His procedure consisted of mobilizing and resecting the complete aganglionic intestines followed by an end-to-end anastomosis of normal colon to the anal canal. Many surgeons, however, faced postoperative problems such as pelvic nerve damage as a consequence of this surgical procedure. Hence, other techniques were introduced, such as the one described by Rehbein.[5] Rehbein's procedure avoided the pelvic nerves by only resecting the upper aganglionic colon. The remaining aganglionic rectum and anal canal were dilated afterwards. This too was not entirely satisfactory and in turn led to newer techniques such as the ones described by Duhamel6 and Soave.[7] Duhamel opted for a retrorectal

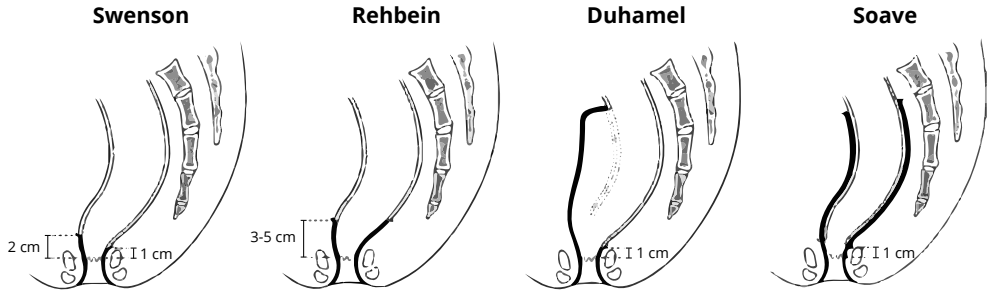

Figure 4

A schematic illustration of four of the most common surgical procedures that use an abdominal approach. Swenson's procedure consists of mobilizing and resecting the complete aganglionic intestines relatively close to the dentate line, followed by an end-to-end anastomosis of healthy colon to the anal canal. Rehbein's procedure consists of resecting the upper aganglionic colon, leaving 3 to 5 cm of distal aganglionic colon in situ, which is usually dilated afterwards. Duhamel's procedure consists of a retrorectal approach followed by a side-to-side anastomosis of healthy colon to the posterior of the aganglionated rectum. Finally, Soave's procedure consists of dissecting a rectal mucosal tube off the submucosal plane after which the ganglionic colon is pulled through the rectal sleeve.

Adapted from Figure 44-1 in the chapter on Hirschsprung Disease. In: Ziegler MM et al, editors. Operative Pediatric Surgery. New York, NY: McGraw-Hill Education; 2014.

approach followed by a side-to-side anastomosis of ganglionic colon to aganglionated rectum thereby completely avoiding the pelvic nerves anterior of the rectum. Soave's solution to avoid damaging the innervation of the pelvic floor was to devise an endorectal pull-through procedure whereby a rectal mucosal tube was dissected off the submucosal plane.

The transanal approach that has gained in popularity over the last few years is the transanal endorectal pull-through (TERPT) described by De la Torre-Mondragón and Ortega in 1998.[59] The TERPT procedure consists of a transanal pull-through of ganglionic intestines followed by a very low, direct anastomosis just above the dentate line (Figure 5).[59] The latter can be done by using a short aganglionic muscular cuff created by a transanal submucosal dissection (Soave-like)[59,60] or by a full-thickness dissection of the bowel wall (Swenson-like).[61] By avoiding extensive manipulation in the peritoneal cavity, this approach is thought to reduce the risk of postoperative adhesions. At the same time damage to the pelvic floor innervation is prevented by avoiding extensive pelvic dissection outside the rectum. Short-term outcomes of this technique seem favorable.

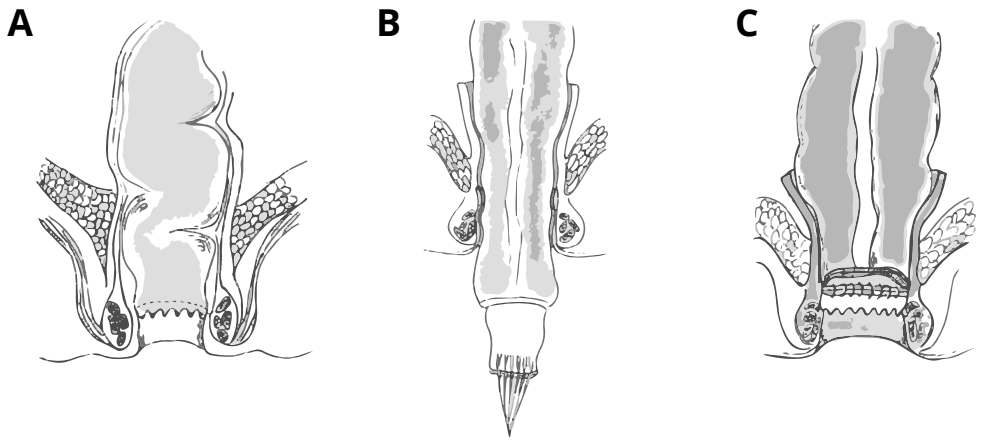

Figure 5
A schematic representation of the transanal endorectal pull-through (TERPT) procedure.
A: The location of the intended transanal circumferential incision, approximately 5 mm above the dentate line, marked by the dotted line.
B: An endorectal dissection is made following the submucosal plane of the rectum until the level of the peritoneal cavity is reached. Next, the division of the muscular rectal wall is continued circumferentially, freeing the intra-abdominal colon from the muscle sleeve. The colon is then pulled through the anus.
C: The pulled-through aganglionic colon is resected and an anastomosis of the healthy colon and the anus is made.
Adapted from Figures 2, 4, and 5 in the article Hirschsprung disease. Haricharan RN, Georgeson KE. Semin Pediatr Surg. 2008 Nov;17(4):266-75.

Some studies reported outcomes comparable to other techniques and other studies even reported better results.[60,62–64] Nevertheless, concerns remain, such as that during the TERPT procedure the anal sphincter may be damaged by overstretching.[65] Despite this concern, a manometric study performed by van Leeuwen and colleagues in 2002, found no differences regarding sphincter functioning between abdominal and transanal approaches.[66] The authors subsequently concluded that the transanal approach did not pose an increased risk of sphincter damage. A more recent study by Stensrud and colleagues, however, showed that sphincter damage and incontinence are in fact seen more often following the anal approach in comparison to the abdominal approach.[67] It is important to note, however, that for this technique extensive long-term clinical results are not yet available. It remains to be seen what the impact of the different surgical approaches is on long-term anorectal functioning and fecal continence.

LONG-TERM OUTCOMES

Despite the best surgical efforts, studies often emphasize that HD is an incurable disease. This is illustrated by various reports reporting that after surgical reconstruction, a large group of patients continue to suffer from defecation disorders, such as constipation and fecal incontinence.[68–72] To date, it is not clear why some patients experience more complaints than others. What is clear, is that these disorders may have far reaching consequences, because both constipation and fecal incontinence are known to negatively influence the quality of life.[73,74]

Constipation

Constipation is the chief complaint of HD patients. Often the complaints are so severe that surgical reconstruction of the affected intestines is required to restore bowel continuity. Without this intervention, intestinal obstruction could eventually lead to abdominal distension, Hirschsprung's disease-associated enterocolitis, growth failure, and in severe cases, mortality. Even after surgical reconstruction, however, the majority of HD patients retain a lifelong tendency towards constipation.

The tendency towards constipation may have several causes. First, and most importantly, patients with HD will never develop a functional rectoanal inhibitory reflex.[19–21] This reflex and subsequent relaxation of the internal anal sphincter are vital for the smooth passage of stool. Second, incomplete resection may result in residual aganglionic intestines that could continue to hinder the passage of stool. Last, constipation is a common complaint in the general population with an estimated prevalence of 16%.[75] After excluding secondary causes for constipation, the majority of these complaints can

be explained either as a functional defecation disorder (dyssynergic defecation), slow-transit constipation, or irritable bowel syndrome.[76] On account of the high prevalence of these disorders in the general population, it is likely that these disorders may also play a role in the constipation complaints of HD patients. Further research is necessary to determine to what extent other causes of constipation play a role in the complaints of patients with HD.

Fecal incontinence

Fecal incontinence is a frequent complaint of patients with HD, particularly after surgical reconstruction. The prevalence of fecal incontinence, mostly limited to soiling, in the general population is estimated at approximately 8%,[77] whereas it may be as high as 40% in patients with HD.[78,79] It has been postulated that the fecal incontinence complaints of HD patients may be a consequence of damage to the anal sphincter or innervation of the pelvic floor during surgery, or from a reduced rectal reservoir as a result of surgical reconstruction.[80] There are several known risk factors for poor fecal continence in HD patients, such as total colonic aganglionosis and the combination of HD with Down syndrome.[68,81] Another potential risk factor for fecal incontinence may be constipation in association with fecal incontinence, a phenomenon often seen in pediatric and geriatric populations.[82] Further research on this subject is needed because as the cause for fecal incontinence in the majority of HD patients remains unclear.

Quality of life

Quality of life plays an increasingly important aspect in the assessment of long-term outcomes, especially in chronic illnesses such as HD. Quality of life is a broad concept, subjective by definition. It is often subdivided into various domains, often including the physical, psychosocial, and social domains, as well as environment, level of independence, and spirituality. Defecation disorders, such as constipation and fecal incontinence, are known to influence the quality of life.[73,74] The prevalence of these disorders in HD patients is relatively high[68–72] and one may assume that it negatively influences their quality of life. This line of thought has prompted various studies on the long-term functional outcomes and quality of life in HD patients.[70,72,83,84] Unfortunately, it is still unclear how these complaints and their influence on quality of life develop with aging.[83] Additional research is therefore needed to determine how the influence of defecation disorders on quality of life varies in different age groups.

AIMS OF THIS THESIS

Both the diagnosis and treatment of HD have improved vastly over the last few decades. Nevertheless, diagnosing HD remains troublesome, especially in very young infants. Recent studies have shown that the rectal suction biopsy is not entirely satisfactory and that caution is required when interpreting the outcome. Although surgical techniques are being perfected and outcomes are improving, proper follow-up studies are necessary to assess the differences between the various techniques in terms of long-term functional outcomes and quality of life.

From this follows the twofold aim of this thesis. First, to improve the diagnostic process of determining HD with the aim to increase accuracy and to reduce the number of invasive biopsy procedures. Second, to perform long-term follow-up studies of HD patients to assess their functional outcomes and quality of life.

The first part of this thesis focusses on the diagnostic process of determining HD, starting with a study on the accuracy of rectal suction biopsies in **Chapter 2**. For this study we investigated, in retrospect, all rectal suction biopsies performed at University Medical Center Groningen between 1975 and 2011, and analyzed at what age rectal suction biopsies gave an accurate diagnosis. On the basis of this study we hypothesized that anorectal manometry could be both a viable and safe screening tool for HD, and that it could be used to reduce the number of invasive rectal suction biopsy procedures in the diagnosis of HD. Prospectively, we gathered the results of 105 patients suspected of HD who had undergone anorectal manometry. The results of this study are presented and discussed in **Chapter 3**. In our study on anorectal manometry we found that even in patients with normally developed ganglion cells, that is patients in whom HD was excluded on the basis of rectal suction biopsy, the rectoanal inhibitory reflex could be absent at birth. We hypothesized that the absence of this reflex might play a role in the constipation complaints experienced by these patients. In addition, we hypothesized that this reflex might mature and develop after birth. The development of this reflex in newborns and its role with regards to constipation complaints are discussed in **Chapter 4**. In **Chapter 5**, the last chapter in this part of the thesis, we describe two extraordinary cases of HD. In these two patients the disease had gone unnoticed until adolescence, when they both presented with a solitary rectal ulcer.

The second aim of this thesis is to assess the long-term functional outcomes of HD patients. Traditionally, the main outcome parameters in the treatment of HD are constipation and fecal incontinence, that is, the inability to evacuate and retain stool. Unfortunately, the questionnaires currently available for assessing these complaints are often limited in the number of items and focus on quality of life rather than on factors

that influence anorectal functioning.[85–90] The second part of this thesis is therefore dedicated to the detailed questionnaire we developed to assess anorectal functioning. The contents, applicability, and validity of the questionnaire are explained in **Chapter 6**. To obtain reference data for our study on HD patients, we performed an extensive survey of the Dutch population, the analysis of which is presented in **Chapter 7**.

The third and last part of this thesis focuses on the long-term outcomes of HD patients. Based on our clinical observations we hypothesized that a significant number of HD patients who reach adulthood continue to experience functional complaints such as constipation and fecal incontinence. To test this hypothesis we performed a study together with all six pediatric surgery institutes in the Netherlands. The resulting nation-wide, cross-sectional study consisted of investigating the medical records of all known HD patients and inviting eligible patients to complete our newly developed questionnaire on anorectal functioning and a questionnaire on quality of life. The results of this study are discussed in **Chapters 8 and 9**. In **Chapter 8** we analyze the results of the anorectal functioning and quality of life questionnaires, with a subanalysis to determine factors associated with poor outcomes, and an analysis on the influence of poor outcomes on quality of life. In **Chapter 9** we use a subgroup of patients collected from the nation-wide study to perform a matched comparison of patients treated with the Duhamel procedure and the TERPT procedure. In the final chapter of this section, **Chapter 10**, we report on a study in which we show that dyssynergic defecation can play an important role in the postoperative constipation complaints of HD patients. We hypothesized that not all postoperative defecation complaints were attributable to HD and that dyssynergic defecation – for which viable treatment options are available – may increase the severity of the constipation in these patients.

Finally, we discuss the main findings of this thesis in a general discussion in **Chapter 11**, thereby reflecting on the hypotheses laid down at the beginning of the thesis. We also discuss the implications of this work and directions for future research. A summary of the main findings and conclusions is given in **Chapters 12 and 13**, in English and Dutch respectively.

REFERENCES

1 Hirschsprung H. Stuhlträgheit Neugeborener in Folge von Dilatation und Hypertrophie des Colons. Jahrb für Kinderheilkd und Phys Erziehung. 1887;27:1–7.

2 Swenson O, Neuhauser EB, Pickett LK. New concepts of the etiology, diagnosis and treatment of congenital megacolon (Hirschsprung's disease). Pediatrics. 1949;4:201–9.

3 Swenson O, Bill AH. Resection of rectum and rectosigmoid with preservation of the sphincter for benign spastic lesions producing megacolon; an experimental study. Surgery. 1948;24:212–20.

4 Whitehouse FR, Kernohan JW. Myenteric plexus in congenital megacolon; study of 11 cases. Arch Intern Med (Chicago, Ill 1908). 1948;82:75–111.

5 Rehbein F. Operative Behandlung der Hirschsprungschen Krankheit. Langenbecks Arch fur Klin Chir. 1953;276:540–3.

6 Duhamel B. A new operation for the treatment of Hirschsprung's disease. Arch Dis Child. 1960;35:38–9.

7 Soave F. Une nouvelle technique chirurgicale pour le traitment de la maladie de Hirschsprung. J Chir (Paris). 1963;86:451–64.

8 Goldstein AM, Hofstra RMW, Burns AJ. Building a brain in the gut: development of the enteric nervous system. Clin Genet. 2013;83:307–16.

9 Wallace AS, Burns AJ. Development of the enteric nervous system, smooth muscle and interstitial cells of Cajal in the human gastrointestinal tract. Cell Tissue Res. 2005;319:367–82.

10 Webster W. Embryogenesis of the enteric ganglia in normal mice and in mice that develop congenital aganglionic megacolon. J Embryol Exp Morphol. 1973;30:573–85.

11 Hoehner JC, Wester T, Pahlman S, et al. Alterations in neurotrophin and neurotrophin-receptor localization in Hirschsprung's disease. J Pediatr Surg. 1996;31:1524–9.

12 Langer JC, Betti PA, Blennerhassett MG. Smooth muscle from aganglionic bowel in Hirschsprung's disease impairs neuronal development in vitro. Cell Tissue Res. 1994;276:181–6.

13 Langer JC. Hirschsprung disease. Curr Opin Pediatr. 2013;25:368–74.

14 Furness JB. Types of neurons in the enteric nervous system. J Auton Nerv Syst. 2000;81:87–96.

15 Watanabe Y, Ito F, Ando H, et al. Extrinsic nerve strands in the aganglionic segment of Hirschsprung's disease. J Pediatr Surg. 1998;33:1233–7.

16 Frigo GM, Tacca M Del, Lecchini S, et al. Some observations on the intrinsic nervous mechanism in Hirschsprung's disease. Gut. 1973;14:35–40.

17 O'Kelly TJ, Davies JR, Tam PK, et al. Abnormalities of nitric-oxide-producing neurons in Hirschsprung's disease: morphology and implications. J Pediatr Surg. 1994;29:294–9.

18 Vizi ES, Zseli J, Kontor E, et al. Characteristics of cholinergic neuroeffector transmission of ganglionic and aganglionic colon in Hirschsprung's disease. Gut. 1990;31:1046–50.

19 Scharli AF. Pathophysiology of Classical Hirschsprung's disease. In: Holschneider AM, Puri P, editors. Hirschsprung's Disease and Allied Disorders. Frankfurt, Germany: Springer; 2000. p. 109–25.

20 Schnaufer L, Talbert JL, Haller JA, et al. Differential sphincteric studies in the diagnosis of ano-rectal disorders of childhood. J Pediatr Surg. 1967;2:538–43.

21 Lawson JO, Nixon HH. Anal canal pressures in the diagnosis of Hirschsprung's disease. J Pediatr Surg. 1967;2:544–52.
22 Rattan SS. The internal anal sphincter: regulation of smooth muscle tone and relaxation. Neurogastroenterol Motil. 2005;17 Suppl 1:50–9.
23 Puri P, Gosemann JH. Variants of Hirschsprung disease. Semin Pediatr Surg. 2012;21:310–8.
24 Ruttenstock E, Puri P. A meta-analysis of clinical outcome in patients with total intestinal aganglionosis. Pediatr Surg Int. 2009;25:833–9.
25 Suita S, Taguchi T, Ieiri S, et al. Hirschsprung's disease in Japan: analysis of 3852 patients based on a nationwide survey in 30 years. J Pediatr Surg. 2005;40:197–201.
26 Best KE, Addor MC, Arriola L, et al. Hirschsprung's disease prevalence in Europe: a register based study. Birth defects Res A, Clin Mol Teratol. 2014;100:695–702.
27 Bradnock TJ, Knight M, Kenny S, et al. Hirschsprung's disease in the UK and Ireland: incidence and anomalies. Arch Dis Child. 2017;102:722-7.
28 Ryan ET, Ecker JL, Christakis NA, et al. Hirschsprung's disease: associated abnormalities and demography. J Pediatr Surg. 1992;27:76–81.
29 Singh SJ, Croaker GD, Manglick P, et al. Hirschsprung's disease: the Australian Paediatric Surveillance Unit's experience. Pediatr Surg Int. 2003;19:247–50.
30 Stensrud KJ, Emblem R, Bjornland K. Late diagnosis of Hirschsprung disease--patient characteristics and results. J Pediatr Surg. 2012;47:1874–9.
31 Doodnath R, Puri P. A systematic review and meta-analysis of Hirschsprung's disease presenting after childhood. Pediatr Surg Int. 2010;26:1107–10.
32 Sharma S, Gupta DK. Hirschsprung's disease presenting beyond infancy: surgical options and postoperative outcome. Pediatr Surg Int. 2012;28:5–8.
33 Zeng M, Amodio J, Schwarz S, et al. Hirschsprung disease presenting as sigmoid volvulus: a case report and review of the literature. J Pediatr Surg. 2013;48:243–6.
34 Moore SW. The contribution of associated congenital anomalies in understanding Hirschsprung's disease. Pediatr Surg Int. 2006;22:305–15.
35 Lorijn F De, Reitsma JB, Voskuijl WP, et al. Diagnosis of Hirschsprung's disease: a prospective, comparative accuracy study of common tests. J Pediatr. 2005;146:787–92.
36 Lorijn F De, Kremer LCM, Reitsma JB, et al. Diagnostic Tests in Hirschsprung Disease : A Systematic Review. J Pediatr Gastroenterol Nutr. 2006;42:496–505.
37 Aldridge RT, Campbell PE. Ganglion cell distribution in the normal rectum and anal canal. A basis for the diagnosis of Hirschsprung's disease by anorectal biopsy. J Pediatr Surg. 1968;3:475–90.
38 Meier-Ruge W, Lutterbeck PM, Herzog B, et al. Acetylcholinesterase activity in suction biopsies of the rectum in the diagnosis of Hirschsprung's disease. J Pediatr Surg. 1972;7:11–7.
39 Nakao M, Suita S, Taguchi T, et al. Fourteen-year experience of acetylcholinesterase staining for rectal mucosal biopsy in neonatal Hirschsprung's disease. J Pediatr Surg. 2001;36:1357–63.
40 Bagdzevicius R, Gelman S, Gukauskiene L, et al. Application of acetylcholinesterase histochemistry for the diagnosis of Hirschsprung's disease in neonates and infants: a twenty-year experience. Medicina (Kaunas). 2011;47:374–9.
41 Kapur RP, Reed RC, Finn LS, et al. Calretinin immunohistochemistry versus acetylcholinesterase histochemistry in the evaluation of suction rectal biopsies for Hirschsprung Disease. Pediatr Dev Pathol. 2009;12:6–15.

42 Guinard-Samuel V, Bonnard A, Lagausie P De, et al. Calretinin immunohistochemistry: a simple and efficient tool to diagnose Hirschsprung disease. Mod Pathol. 2009;22:1379–84.
43 Morris MI, Soglio DB-D, Ouimet A, et al. A study of calretinin in Hirschsprung pathology, particularly in total colonic aganglionosis. J Pediatr Surg. 2013;48:1037–43.
44 de Arruda Lourencao PL, Takegawa BK, Ortolan E V, et al. Does calretinin immunohistochemistry reduce inconclusive diagnosis in rectal biopsies for Hirschsprung disease? J Pediatr Gastroenterol Nutr. 2014;58:603–7.
45 Takawira C, D'Agostini S, Shenouda S, et al. Laboratory procedures update on Hirschsprung disease. J Pediatr Gastroenterol Nutr. 2015;60:598–605.
46 Pini-Prato A, Martucciello G, Jasonni V. Rectal suction biopsy in the diagnosis of intestinal dysganglionoses: 5-year experience with Solo-RBT in 389 patients. J Pediatr Surg. 2006;41:1043–8.
47 Friedmacher F, Puri P. Rectal suction biopsy for the diagnosis of Hirschsprung's disease: a systematic review of diagnostic accuracy and complications. Pediatr Surg Int. 2015;31:821–30.
48 Iwai N, Yanagihara J, Tokiwa K, et al. Reliability of anorectal manometry in the diagnosis of Hirschsprung's disease. Z Kinderchir. 1988;43:405–7.
49 Emir H, Akman M, Sarimurat N, et al. Anorectal manometry during the neonatal period: its specificity in the diagnosis of Hirschsprung's disease. Eur J Pediatr Surg. 1999;9:101–3.
50 Huang Y, Zheng S, Xiao X. Preliminary evaluation of anorectal manometry in diagnosing Hirschsprung's disease in neonates. Pediatr Surg Int. 2009;25:41–5.
51 Noviello C, Cobellis G, Romano M, et al. Diagnosis of Hirschsprung's Disease: an age-related approach in children below or above one year. Colorectal Dis. 2010;12:1044–8.
52 Bradnock TJ, Walker GM. Evolution in the management of Hirschsprung's disease in the UK and Ireland: A national survey of practice revisited. Ann R Coll Surg Engl. 2011;93:34–8.
53 Zani A, Eaton S, Morini F, et al. European Paediatric Surgeons' Association Survey on the Management of Hirschsprung Disease. Eur J Pediatr Surg. 2016;27:96–101.
54 Tang YF, Chen JG, An HJ, et al. High-resolution anorectal manometry in newborns: normative values and diagnostic utility in Hirschsprung disease. Neurogastroenterol Motil. 2014;26:1565–72.
55 Wong CW, Lau CT, Chung PH, et al. The value of the 24-h delayed abdominal radiograph of barium enema in the diagnosis of Hirschsprung's disease. Pediatr Surg Int. 2015;31:11–5.
56 Muller CO, Mignot C, Belarbi N, et al. Does the radiographic transition zone correlate with the level of aganglionosis on the specimen in Hirschsprung's disease? Pediatr Surg Int. 2012;28:597–601.
57 Hoffmann K, Schier F, Waldschmidt J. Laparoscopic Swenson's procedure in children. Eur J Pediatr Surg. 1996;6:15–7.
58 de Lagausie P, Berrebi D, Geib G, et al. Laparoscopic Duhamel procedure. Surg Endosc. 1999;13:972–4.
59 la Torre-Mondragón L De, Ortega-Salgado JA. Transanal endorectal pull-through for Hirschsprung's disease. J Pediatr Surg. 1998;33:1283–6.
60 la Torre L De, Ortega A. Transanal versus open endorectal pull-through for Hirschsprung's disease. J Pediatr Surg. 2000;35:1630–2.
61 Langer JC. Laparoscopic and transanal pull-through for Hirschsprung disease. Semin Pediatr Surg. 2012;21:283–90.
62 Tannuri ACA, Tannuri U, Romão RLP. Transanal endorectal pull-through in children with

Hirschsprung's disease—technical refinements and comparison of results with the Duhamel procedure. J Pediatr Surg. 2009;44:767–72.
63 Stensrud KJ, Emblem R, Bjørnland K. Functional outcome after operation for Hirschsprung disease—transanal vs transabdominal approach. J Pediatr Surg. 2010;45:1640–4.
64 Giuliani S, Betalli P, Narciso A, et al. Outcome Comparison Among Laparoscopic Duhamel, Laparotomic Duhamel, and Transanal Endorectal Pull-Through: A Single-Center, 18-Year Experience. J Laparoendosc Adv Surg Tech. 2011;21:859–63.
65 El-Sawaf MI, Drongowski RA, Chamberlain JN, et al. Are the long-term results of the transanal pull-through equal to those of the transabdominal pull-through? A comparison of the 2 approaches for Hirschsprung disease. J Pediatr Surg. 2007;42:41–7.
66 van Leeuwen K, Geiger JD, Barnett JL, et al. Stooling and manometric findings after primary pull-throughs in Hirschsprung's disease: Perineal versus abdominal approaches. J Pediatr Surg. 2002;37:1321–5.
67 Stensrud KJ, Emblem R, Bjornland K. Anal endosonography and bowel function in patients undergoing different types of endorectal pull-through procedures for Hirschsprung disease. J Pediatr Surg. 2015;50:1341–6.
68 Menezes M, Corbally M, Puri P. Long-term results of bowel function after treatment for Hirschsprung's disease: a 29-year review. Pediatr Surg Int. 2006;22:987–90.
69 Ieiri S, Nakatsuji T, Akiyoshi J, et al. Long-term outcomes and the quality of life of Hirschsprung disease in adolescents who have reached 18 years or older—a 47-year single-institute experience. J Pediatr Surg. 2010;45:2398–402.
70 Jarvi K, Laitakari EM, Koivusalo A, et al. Bowel function and gastrointestinal quality of life among adults operated for Hirschsprung disease during childhood: a population-based study. Ann Surg. 2010;252:977–81.
71 Aworanti OM, McDowell DT, Martin IM, et al. Does Functional Outcome Improve with Time Postsurgery for Hirschsprung Disease? Eur J Pediatr Surg. 2015;26:192–9.
72 Niramis R, Watanatittan S, Anuntkosol M, et al. Quality of life of patients with Hirschsprung's disease at 5 - 20 years post pull-through operations. Eur J Pediatr Surg. 2008;18:38–43.
73 Bartlett L, Nowak M, Ho Y-H. Impact of fecal incontinence on quality of life. World J Gastroenterol. 2009;15:3276–82.
74 Belsey J, Greenfield S, Candy D, et al. Systematic review: Impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther. 2010;31:938–49.
75 Mugie SM, Benninga MA, Lorenzo C Di. Epidemiology of constipation in children and adults: A systematic review. Best Pract Res Clin Gastroenterol. 2011;25:3–18.
76 Sharma A, Rao S. Constipation: Pathophysiology and Current Therapeutic Approaches. In: Handbook of experimental pharmacology. 2016. p. 59–74.
77 Whitehead WE, Borrud L, Goode PS, et al. Fecal Incontinence in US Adults: Epidemiology and Risk Factors. Gastroenterology. 2009;137:512–517.e2.
78 Catto-Smith AG, Trajanovska M, Taylor RG. Long-term continence after surgery for Hirschsprung's disease. J Gastroenterol Hepatol. 2007;22:2273–82.
79 Neuvonen MI, Kyrklund K, Rintala RJ, et al. Bowel Function and Quality of Life After Transanal Endorectal Pull-through for Hirschsprung Disease: Controlled Outcomes up to Adulthood. Ann Surg. 2017;265:622–9.
80 Heikkinen M, Rintala R, Luukkonen P. Long-term anal sphincter performance after surgery for Hirschsprung's disease. J Pediatr Surg. 1997;32:1443–6.
81 Moore SW. Total colonic aganglionosis in Hirschsprung disease. Semin Pediatr Surg.

2012;21:302–9.
82 Nurko S, Scott SM. Coexistence of constipation and incontinence in children and adults. Best Pract Res Clin Gastroenterol. 2011;25:29–41.
83 Hartman EE, Oort FJ, Aronson DC, et al. Quality of life and disease-specific functioning of patients with anorectal malformations or Hirschsprung's disease: a review. Arch Dis Child. 2011;96:398–406.
84 Collins L, Collis B, Trajanovska M, et al. Quality of life outcomes in children with Hirschsprung disease. J Pediatr Surg. 2017;52:2006-10.
85 Eypasch E, Williams JI, Wood-Dauphinee S, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. Br J Surg. 1995;82:216–22.
86 Osterberg A, Graf W, Karlbom U, et al. Evaluation of a questionnaire in the assessment of patients with faecal incontinence and constipation. Scand J Gastroenterol. 1996;31:575–80.
87 Frank L, Kleinman L, Farup C, et al. Psychometric validation of a constipation symptom assessment questionnaire. Scand J Gastroenterol. 1999;34:870–7.
88 Hanneman MJ, Sprangers MA, De Mik EL, et al. Quality of life in patients with anorectal malformation or Hirschsprung's disease: development of a disease-specific questionnaire. Dis Colon Rectum. 2001;44:1650–60.
89 Lehur P-A, Zerbib F, Neunlist M, et al. Comparison of quality of life and anorectal function after artificial sphincter implantation. Dis Colon Rectum. 2002;45:508–13.
90 Adelstein B-A, Irwig L, Macaskill P, et al. A self administered reliable questionnaire to assess lower bowel symptoms. BMC Gastroenterol. 2008;8:8.

PART I

Early diagnosis of Hirschsprung's disease

CHAPTER 2

Infant's age influences the accuracy of rectal suction biopsies for diagnosing of Hirschsprung's disease

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SUMMARY

Background

Hirschsprung's disease (HD) is a rare birth defect of the distal colon. Analysis of rectal suction biopsy (RSB) is considered to be the most reliable method for its diagnosis in infants. However, the diagnostic accuracy of RSB analysis could be affected by the patient's age, possibly because of rapid development of the enteric nervous system in the first weeks after birth. Because there is a trend toward testing for HD at early ages, we aimed to determine whether the diagnostic accuracy of RSB analysis is associated with the patient's age.

Methods

We performed a retrospective analysis of all patients from whom one or more RSBs were analyzed from 1975 through 2011 (529 RSBs from 441 patients). Outcomes of RSB analyses were categorized as positive, inconclusive, or negative for HD. Primary diagnoses, based only on RSB, were compared with final diagnoses made after at least one year of clinical follow-up. Age at time of RSB analysis was corrected for the gestational age. By using these criteria, we determined the diagnostic accuracy of RSB analysis for different age groups.

Results

RSB analysis identified HD in patients with sensitivity values of 46% (patients –45 to 7 days old), 47% (8–22 days old), and 62% (23–39 days old) (corrected for gestational age). The average sensitivity with which RSB analysis identified HD in patients older than 39 days was 88%. RSB identified HD in patients younger than 39 days old with significantly lower sensitivity than in older patients (50% vs 88%, $P < .001$). The specificity with which RSB identified infants without HD was not affected by age (average 95%). Of all RSBs, 11% were inconclusive for the diagnosis of HD.

Conclusions

RSB analysis identifies HD in patients younger than 39 days old with only 50% sensitivity. Moreover, RSBs obtained from younger patients often lead to inconclusive outcomes and require additional biopsies. We propose that for infants suspected of HD at these ages, a noninvasive technique, such as anorectal manometry, should be used for a primary diagnosis. RSB should thereafter be used to confirm the diagnosis when the infant is older than 39 days.

INTRODUCTION

Hirschsprung's disease (HD) is a relatively rare birth defect of the distal colon. It is characterized by aganglionosis, *i.e.* the absence of ganglion cells in the enteric nervous system. At the same time, these patients also miss the rectoanal inhibitory reflex due to aganglionosis in the internal sphincter complex.[1] The incidence of HD is estimated to be approximately 1 in 5000 live births.[2] Children with constipation complaints, who are suspected of having HD, are seen far more often.

While clinical presentation can only suggest HD, the final diagnosis must be confirmed by the outcomes of rectal suction biopsy (RSB), contrast enema, and/or anorectal manometry. All three tests have been shown to have similar sensitivity and specificity, with the RSB being the most reliable.[3] Anorectal manometry and contrast enema were previously described as difficult to interpret in the neonatal period.[4–8] Additionally, recently, Bagdzevicius and colleagues[9] reported that RSB too is not an entirely satisfactory method for diagnosing HD in neonates since its outcome may be affected by the patient's age. A possible explanation for these diagnostic obstacles is the dynamic increase of hypertrophic nerve fibers during the first weeks after birth.[10] These nerve fibers are of an extrinsic origin. In HD patients they become hypertrophic and proliferate due to a failure to connect with the intrinsic, enteric nervous system. Both the intrinsic absence of ganglion cells and hypertrophy with proliferation of extrinsic nerve fibers can be used in diagnosing HD. Currently, there is a trend towards diagnosing HD increasingly early, with the majority of patients already tested during the neonatal period.[11] While this trend is thought to decrease the risk of life threatening Hirschsprung's-associated enterocolitis,[12] it may at the same time introduce the risk of misdiagnosing HD.

Furthermore, we also observed that the diagnosis of HD is often very troublesome in newborns. On the basis of this clinical experience, combined with the knowledge from scientific literature, we hypothesized that the outcome of the RSB could be dependent on the age of the patient. The aim of this study was, therefore, to determine at which age RSB provides an accurate diagnosis.

METHODS

Data collection

A retrospective analysis was conducted on suspected HD patients who had undergone one or more rectal suction biopsies (RSBs) between 1975 and 2011 at University Medical Center Groningen. Indications for performing a RSB were: delayed meconium passage, distended abdomen, difficult spontaneous defecation, and/or signs of Hirschsprung's-

associated enterocolitis. The age at which the RSBs were obtained was corrected for the infant's gestational age. A full term age of 40 weeks was considered normal. During the study period five pathologists with several years' experience in academic gastrointestinal pathology and who were familiar with the diagnosis of HD examined the RSBs. The pathologists succeeded each other over the years, wherein a maximum of two pathologists were responsible for the analysis of RSBs at any given time. RSBs were excluded from the main statistical analysis if the pathology report stated that the RSB was inappropriate for diagnosing HD. In these patients the RSB contained insufficient submucosa or anal epithelium. The RSBs that yielded sufficient tissue were either classified as positive for HD (no ganglion cells and/or increased nerve fiber proliferation), inconclusive for HD (no ganglion cells and little or no nerve fiber proliferation), or negative for HD (ganglion cells and little or no increased nerve fiber proliferation). In order to find possible factors that contributed to the diagnostic accuracy of the RSB outcomes we analyzed the RSBs that had been rejected by the pathologists due to insufficient tissue.

RSB and staining procedures

Prior to obtaining a RSB, the patient was given a cleansing enema. Subsequently, rectal tissue consisting of mucosal and submucosal material was extracted using the rectal suction biopsy tube, specially designed for use in HD.[13] The RSB procedure was performed without sedation or anesthesia, unless it was required for other another procedure. In all patients the RSB procedure consisted of extracting specimens at three levels between 2 and 10 cm, varying between physicians, above the anal verge (*e.g.* 3, 4.5, and 6 cm). The specimens were frozen and examined at, on average, six levels at 200 µm intervals. At each interval a 10 µm thick section was stained by hematoxylin and eosin (H&E), reduced nicotinamide adenine dinucleotide (NADH) enzyme histochemistry, and acetylcholinesterase (AChE) enzyme histochemistry. The presence of ganglion cells excluded the diagnosis Hirschsprung's disease. Hypertrophy or hyperplasia of extrinsic cholinergic nerve fibers in the submucosa, muscularis mucosa, and/or mucosa together with the absence of ganglion cells, was regarded as compatible with Hirschsprung's disease. NADH histochemistry (Roche, Switzerland) was performed in combination with tetrazolium reductase (Sigma, United Kingdom), as was reported elsewhere.[14] The AChE histochemistry staining technique was applied according to a modified version of the method described by Karnovsky and Roots.[15]

Analysis of the RSB data

We compared the diagnosis based on the primary RSB to the final diagnosis made after at least one year of clinical follow-up. The final diagnosis was based on the clinical

condition of the patient, additional RSB results, anorectal manometry and/or resected colon pathology. An exclusion factor for HD was the presence of a functioning rectoanal inhibitory reflex as determined by anorectal manometry. The RSB outcomes were classified as true positive, false positive, true negative, or false negative on the basis of the final diagnosis.

In order to analyze the RSB outcomes at different ages, we divided the patients into ten groups on the basis of their age percentiles: -45 to 7, 8 to 22, 23 to 39, 40 to 53, 54 to 78, 79 to 108, 109 to 160, 161 to 246, 247 to 335, and 336 to 6390 days of age (corrected for gestational age). The sensitivity and specificity of the RSB were calculated separately for each age group. We also determined the probability of a correct HD diagnosis based on the age at which the RSBs were obtained.

Statistical analysis

Data were analyzed with SPSS 20.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY). The statistical tests that were used were limited to Pearson's chi-square test, Student's *t*-test, and Mann-Whitney *U*-test, which were all used when the requirements were met. Sensitivity and specificity of the test were calculated using the classification mentioned above, as appropriate. Predictive values were calculated with the same classifications, as is conventional. The probability was defined by the number of true positive RSB outcomes. The relationship between age and the probability of a correct diagnosis was evaluated by spline regression analysis using Stata 11 (StataCorp, College Station, TX). Two-sided *P* values of less than .050 were considered statistically significant.

Table 1
Patient characteristics

Patients who underwent a RSB (n)	441
One RSB needed for accurate diagnosis (%)	83%
Multiple RSBs needed for accurate diagnosis (%)	17%
Patients ultimately diagnosed with HD (n)	190
Total number of RSBs obtained (n)	559
Included (sufficient) RSBs (n)	529
Excluded (insufficient) RSBs (n)	30
Median age at time of RSB (days)*	78 (-45 – 6390)

HD = Hirschsprung's disease, RSB = rectal suction biopsy
* Median (minimum – maximum)

RESULTS

Patient characteristics

Out of a total of 559 RSBs obtained between 1975 and 2011, we excluded 5.4% (n = 30) because insufficient tissue had been extracted (Table 1). Hence, we included 529 RSB outcomes obtained, from 441 patients in our analyses. Patients' ages at the time of the biopsies ranged from -45 days in the youngest to 6390 days, *i.e.* 17 years and 6 months, in the oldest. The median age was 78 days. Based on clinical follow-up, additional RSBs, anorectal manometry, or pathology of the resected colon, we diagnosed 43% of the patients (n = 190) with HD after at least one year of follow-up. In 57% of the patients (n = 251) we excluded HD. Out of the 441 patients who had undergone RSBs, 17% (n = 74) required one to three additional RSBs to arrive at an accurate diagnosis. The highest number of additional RSBs that were necessary to either confirm or exclude HD was observed in the group of 8 to 22-day-olds, and the lowest in the group of 161 to 246-day-olds (Figure 1, $P < .001$).

Patients' age determines the sufficiency of rectal suction biopsy material

Irrespective of patients' ages, 5.4% (n = 30) of the RSBs had to be excluded because insufficient tissue had been extracted. In order to identify the possible risk factors of RSBs that provided insufficient tissue, we compared the excluded RSB data with the

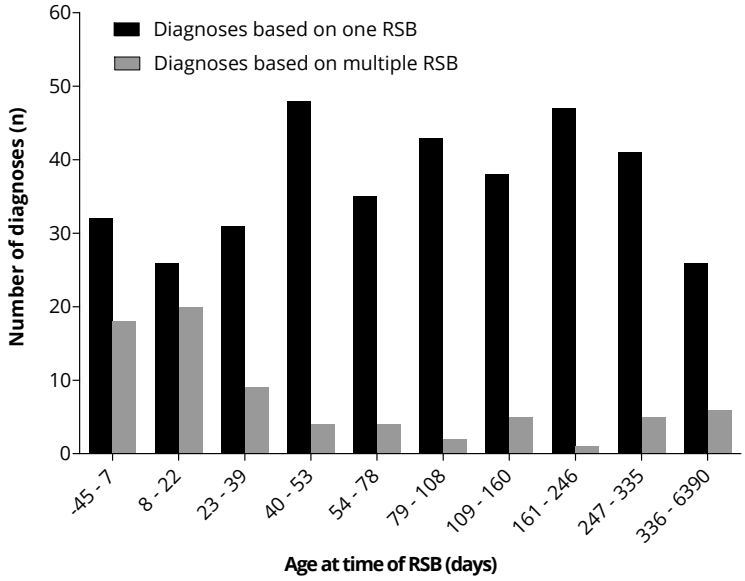

Figure 1
The number of single (black) or additional (white) RSBs needed to confirm or exclude the diagnosis of HD at different age groups ($P < .001$).

Table 2
Accuracy of RSB at different ages

Ages of patients at time of RSB (days)	No. of RSBs per group (n)	RSBs obtained in HD patients					RSBs obtained in non-HD patients				
		True positive	Inconclusive	False negative	Total	Sensitivity (%)	True negative	Inconclusive	False positive	Total	Specificity (%)
-45 - 7	55	17	12	8	37	**46**	18	0	0	18	**100**
8 - 22	54	21	15	9	45	**47**	8	1	0	9	**89**
23 - 39	50	18	5	6	29	**62**	20	1	0	21	**95**
40 - 53	54	25	2	1	28	**89**	24	2	0	26	**92**
54 - 78	53	20	3	2	25	**80**	27	1	0	28	**96**
79 - 108	52	22	0	0	22	**100**	29	1	0	30	**97**
109 - 160	53	12	2	1	15	**80**	37	1	0	38	**97**
161 - 246	54	17	0	0	17	**100**	37	0	0	37	**100**
247 - 335	52	7	2	0	9	**78**	38	4	1	43	**88**
336 - 6390	52	33	5	0	38	**88**	13	1	0	14	**93**
	529	192	46	27	265	**72**	251	12	1	264	**95**

HD = Hirschsprung's disease, RSB = rectal suction biopsy

remaining RSB data that did consist of sufficient tissue. We found a statistically significant difference (P = .033) in age of obtaining the RSBs between the excluded RSBs and the included RSBs: median 43 days (interquartile range, 13-114) in insufficient RSBs versus 78 days (interquartile range, 30-190) in sufficient RSBs. Moreover, we found that insufficient tissue had been extracted significantly more often in patients without HD than in patients with HD (8.3% versus 3.0%, P = .013).

Accuracy of rectal suction biopsy at different ages

We described the accuracy of the RSB for diagnosing HD correctly in terms of three parameters; sensitivity, specificity, and probability.

The overall sensitivity of the RSB outcomes, irrespective of age, was 72% (Table 2). The sensitivity did not change significantly over the studied period of 36 years (Figure 2, P = .315). In patients aged -45 to 7, 8 to 22, and 33 to 39 days, HD was correctly diagnosed on the basis of RSB outcomes in 46%, 47%, and 62% cases, respectively. In patients older than 39 days, the lowest sensitivity of RSB outcomes was 78% in the group of 247 to 335-day-olds. A sensitivity of 100% was reached in the groups of 79 to 108-day-olds and 161 to 246-day-olds.

Based on these observations we decided to continue our analysis of sensitivity in two age groups: the RSB obtained from patients younger than 39 days and those of patients older than 39 days. Subsequently, we observed that the sensitivity of RSB obtained from patients younger than 39 days was significantly lower than the sensitivity for patients older than 39 days (50% versus 88%, P < .001, Table 3).

We found no significant difference in specificity among the age groups investigated (Table 2). The average specificity of the ten groups combined was 95%.

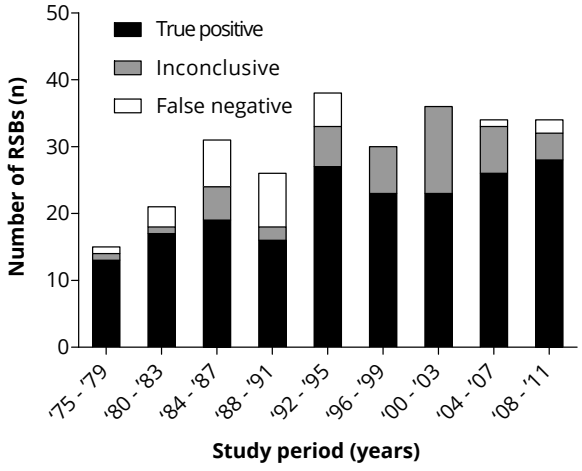

Figure 2
The accuracy of RSBs obtained from HD patients in consecutive study periods.

Because we found that the sensitivity of RSB tended to increase with increasing age, we decided to determine the probability of an accurate HD diagnosis at different ages. The probability of an accurate HD diagnosis was plotted against the age at the time the RSB was obtained (Figure 3). We found a gradual increase in probability up to a maximum value at approximately 125 days (Figure 3A). After the initial increase of probability we found an evidently decreasing trend as patients' ages increased (Figure 3B).

Inconclusive rectal suction biopsy outcomes

Unfortunately, 11.0% of the RSB outcomes were inconclusive (Table 2). The highest number of inconclusive outcomes was obtained from 8 to 22-day-old infants (3.2%). We found the lowest ratio of inconclusive outcomes (0.2%-0.6%) in older infants, *i.e.* 79- to 246-day-olds. If the pathologist had classified a RSB outcome as inconclusive for HD, it had a predictive value of 79% for eventually confirming HD.

Twelve RSB outcomes from eleven different patients were inconclusive for HD and were ultimately diagnosed as non-Hirschsprung (Table 2). Nevertheless, a redo of RSBs was required in seven patients to exclude HD beyond all doubt in these cases. Two patients, in whom the primary HD diagnoses were inconclusive, had complete resolution of defecation complaints after a difficult start. As a consequence, no additional diagnostic tests needed to be administered. The tenth patient underwent two RSBs, on the basis of which he was suspected of having an ultra-short variant of HD. This patient subsequently underwent a lateral sphincterectomy to remedy his persistent constipation complaints.

Table 3
The RSB outcomes for two different age groups

Diagnosis	Outcome	RSBs, ≤ 39 days of age	RSBs, ≥ 40 days of age	*P* value
HD patients	True positive RSBs (n)	56/111 (50%[a])	136/154 (88%[a])	< .001
	Inconclusive RSBs (n)	32/111 (29%)	14/154 (9%)	< .001
	False negative RSBs (n)	23/111 (21%)	4/154 (3%)	< .001
Non-HD patients	True negative RSBs (n)	46/48 (96%[b])	205/216 (95%[b])	NS
	Inconclusive RSBs (n)	2/48 (4%)	10/216 (5%)	NS
	False positive RSBs (n)	0/48 (0%)	1/216 (0%)	NS

HD = Hirschsprung's disease, RSBs = rectal suction biopsies
a Sensitivity
b Specificity

Unfortunately, both the RSB outcomes were inconclusive, and the diagnosis turned out to be a false positive, since the anorectal function tests performed at the age of nine years showed a functioning rectoanal inhibitory reflex. In the eleventh patient for whom the HD diagnosis was inconclusive, the rectoanal inhibitory reflex was found to be absent by anorectal manometry when he was two years old. The outcomes of the RSB and anorectal manometry led to the conclusion to perform a Duhamel reconstruction. Pathological examination following surgery showed the presence of ganglion cells at both the distal and the proximal ends. Although an ultra-short variant of HD in this last patient could not be ruled out completely by the pathological findings, it is more likely that the RSB outcomes were not conclusive enough for making an accurate diagnosis.

False positive rectal suction biopsy outcomes

We had only one false positive RSB outcome. This RSB showed no ganglion cells at 3 and 4.5 cm and hypertrophy with proliferation of nerve fibers at 3, 4.5, and 6 cm. We suspected a shorter variant of HD. Later, this diagnosis had to be corrected. Anorectal function testing at the age of 18 years showed a functioning rectoanal inhibitory reflex. Fortunately, this patient had not undergone any surgery. Instead, he had received conservative treatment in the form of laxatives and daily rectal flushing following the diagnosis of HD based on RSB outcome.

DISCUSSION

In this study we demonstrate for the first time that a patient's age influences the accuracy of RSBs for diagnosing HD disease. The sensitivity of the RSB outcomes, in particular, was significantly lower when the RSBs were obtained in patients younger than 39 days. Moreover, the probability of a correct HD diagnosis increased gradually with increasing age and reached a maximum at approximately 125 days (Figure 3A). In contrast, the specificity of RSB outcomes was not influenced by age and remained high (95%) in all the age groups we investigated.

Several factors can influence the sensitivity of RSB outcomes, like varying biopsy sites, technical issues to do with the staining procedures, and the amount of experience of the pathologist. These factors, however, do not account for the difference in sensitivity in relation to age. We believe that the influence of age resulted from the immaturity of the enteric nervous system, which is still dynamically developing, and therefore quickly changing after birth. This aspect was also mentioned by Nakao and colleagues,[10] who demonstrated that nerve fibers continue to proliferate even after a child is born with HD. Thus, the developmental characteristics of AChE activity, related to changes in

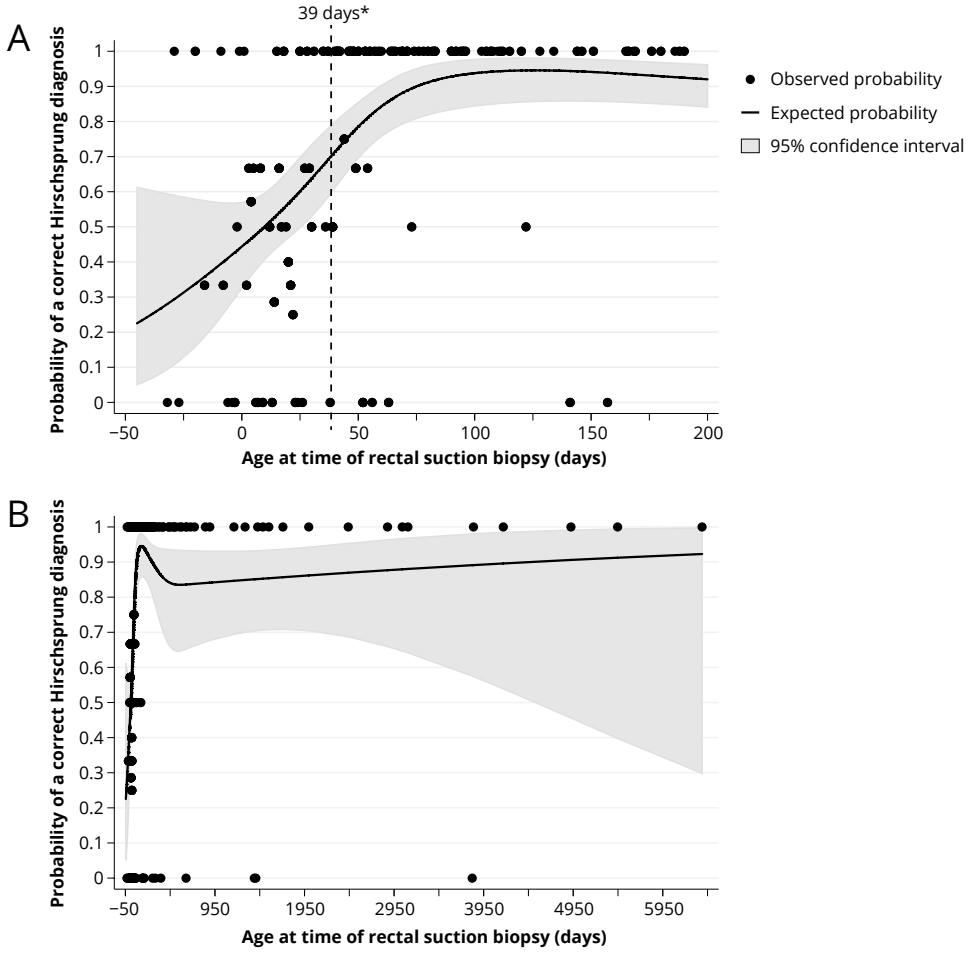

Figure 3

The probability of a correct HD diagnosis plotted against the age at the time of the RSB. Probability was defined as the number of true positive RSB outcomes.

A: RSBs obtained at the ages -45 to 200 days (corrected for gestational age). Probability increased and reached a maximum of 0.95 at the age of approximately 125 days.

B: RSBs obtained at the ages -45 to 6390 days (corrected for gestational age). A slight decrease of probability down to 0.85 was observed after the initial increase at the youngest age.

* The line at 39 days depicts the cutoff point at which we observed a significant difference in the sensitivity between groups younger than 39 days and groups older than 39 days ($P < .001$).

the density of nerve fibers, results in a different staining pattern in younger patients before the classic pattern, characteristic of HD as seen in older patients, has had time to develop.[16] On the one hand one could, therefore, argue that AChE enzyme histochemistry should be reconsidered since it may be responsible for the lower sensitivity of RSB outcomes in younger patients. On the other hand, however, it was reported that AChE enzyme histochemistry greatly increases the specificity of RSB outcomes and reaches a maximum of 98%.[17] Our results do indeed confirm that staining with AChE enzyme histochemistry, combined with NADH enzyme histochemistry and routine H&E staining, resulted in a high average specificity of 95% in all the age groups we investigated. The specificity we found was comparable to the findings reported by other authors.[3,18,19] In addition, we demonstrate that age does not have a statistically significant influence on the specificity of RSB outcomes. Nevertheless, we did observe that there remains a small risk of obtaining a false positive RSB outcome that could lead to an incorrect diagnosis, redundant treatment, and potentially even to unnecessary surgical intervention.

Interestingly, it has been reported that insufficient tissue required for analysis was obtained significantly more often in the case of RSBs in patients who were older than three years.[20] The insufficiency of material in the older group of patients might be a result of the fact that submucosal tissue in older children is more fibrous, which makes it more rigid and, therefore, more difficult to extract through suction.[21] In our study, we indeed observed a steady decrease of sensitivity after the age of 125 days (Figure 3B), a finding which could be explained in terms of the aforementioned reason. Nevertheless, the RSBs obtained from patients older than 125 days, were not deemed inadequate by the pathologist because insufficient tissue had been extracted. Instead, these were classified as inconclusive for diagnosing HD accurately. It would, therefore, seem important to critically define the quality of RSBs in older patients, especially if sufficient submucosal tissue was obtained to assess the presence of ganglion cells.

Furthermore, we found that the RSBs that were excluded due to insufficient tissue, were obtained from patients of a statistically significant younger age than the RSBs that yielded sufficient tissue (43 days in insufficient biopsies versus 78 days in sufficient biopsies, $P = .033$). A reason for this discrepancy remains unclear. Also, RSBs yielding insufficient tissue were seen significantly more often in non-Hirschsprung patients than in HD patients (8.3% versus 3.0%, $P = .013$). This difference might be explained by the fact that technically it is easier to perform RSBs in HD patients due to constant contractions of their rectal wall. Additional studies are required, however, to confirm this theoretical explanation.

As mentioned in the results, a total of 12 RSB taken from 11 patients were inconclusive for HD, with the advice of the pathologist to repeat the RSB. Possibly, the biopsies were

obtained from a faulty location. It is generally accepted that the most distal 1 to 2 cm of the rectum are hypoganglionotic.[22] Accidental RSBs at this height could lead the pathologist to misdiagnose an ultra-short variant of HD.

In our study only one patient had a false positive diagnosis of HD. Anorectal manometry at the age of 18 years revealed the presence of a functioning rectoanal inhibitory reflex. It is generally accepted that the absence of this reflex is a distinguishing feature of HD.[1] It has been postulated that false positive and inconclusive RSB outcomes in healthy children might be due to unspecific AChE staining of AChE in red blood cells membranes in hemorrhagic tissue.[23,24] As a consequence, AChE staining performed on tissue obtained from a hemorrhagic specimen could be unspecific and, therefore, lead to the misinterpretation of RSB outcomes.

Possible clinical implications

Based on our study and literature, we reckon that RSBs obtained from patients younger than 39 days (corrected for gestational age) should be analyzed with the utmost care since it seems that there is no gold standard below this age. Since in the youngest patients RSB outcomes reached a maximum sensitivity of 62%. Moreover, obtaining RSBs is an invasive technique with a small risk of complications. In case of suspected HD, therefore, we would rather choose a noninvasive technique to make the primary diagnosis. Subsequently, a RSB could be obtained to confirm this diagnosis once the infant is older than 39 days. None of the conventional tools currently used to diagnose HD are ideal. Nevertheless, since anorectal manometry is a noninvasive technique and has little to no adverse effects, we propose using it as the screening tool in patients younger than 39 days of age. By so doing, an invasive RSB is avoided if a functioning rectoanal inhibitory reflex is found by anorectal manometry.

Conclusions

As we hypothesized, the outcomes of RSBs obtained below the age of 39 days have a significantly lower sensitivity for diagnosing HD. Additionally, RSB obtained from younger patients often lead to inconclusive outcomes and require additional biopsies. If possible, performing RSBs in patients younger than 39 days should be avoided and, if the RSBs obtained below this age are negative or inconclusive for HD, they should be repeated if the symptoms of the patient persist.

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REFERENCES

1 Scharli AF. Pathophysiology of Classical Hirschsprung's disease. In: Holschneider AM, Puri P, editors. Hirschsprung's Disease and Allied Disorders. Frankfurt, Germany: Springer; 2000. p. 109–25.

2 Suita S, Taguchi T, Ieiri S, et al. Hirschsprung's disease in Japan: analysis of 3852 patients based on a nationwide survey in 30 years. J Pediatr Surg. 2005;40:197–201.

3 Lorijn F De, Reitsma JB, Voskuijl WP, et al. Diagnosis of Hirschsprung's disease: a prospective, comparative accuracy study of common tests. J Pediatr. 2005;146:787–92.

4 Rosenfield NS, Ablow RC, Markowitz RI, et al. Hirschsprung disease: accuracy of the barium enema examination. Radiology. 1984;150:393–400.

5 Iwai N, Yanagihara J, Tokiwa K, et al. Reliability of anorectal manometry in the diagnosis of Hirschsprung's disease. Z Kinderchir. 1988;43:405–7.

6 Emir H, Akman M, Sarimurat N, et al. Anorectal manometry during the neonatal period: its specificity in the diagnosis of Hirschsprung's disease. Eur J Pediatr Surg. 1999;9:101–3.

7 Diamond IR, Casadiego G, Traubici J, et al. The contrast enema for Hirschsprung disease: predictors of a false-positive result. J Pediatr Surg. 2007;42:792–5.

8 Garcia R, Arcement C, Hormaza L, et al. Use of the recto-sigmoid index to diagnose Hirschsprung's disease. Clin Pediatr (Phila). 2007;46:59–63.

9 Bagdzevicius R, Gelman S, Gukauskiene L, et al. Application of acetylcholinesterase histochemistry for the diagnosis of Hirschsprung's disease in neonates and infants: a twenty-year experience. Medicina (Kaunas). 2011;47:374–9.

10 Nakao M, Suita S, Taguchi T, et al. Fourteen-year experience of acetylcholinesterase staining for rectal mucosal biopsy in neonatal Hirschsprung's disease. J Pediatr Surg. 2001;36:1357–63.

11 Singh SJ, Croaker GD, Manglick P, et al. Hirschsprung's disease: the Australian Paediatric Surveillance Unit's experience. Pediatr Surg Int. 2003;19:247–50.

12 Teitelbaum DH, Qualman SJ, Caniano DA. Hirschsprung's disease. Identification of risk factors for enterocolitis. Ann Surg. 1988;207:240–4.

13 Noblett HR. A rectal suction biopsy tube for use in the diagnosis of Hirschsprung's disease. J Pediatr Surg. 1969;4:406–9.

14 Dudorkinova D, Skaba R, Lojda Z, et al. Application of NADH tetrazolium reductase reaction in perioperative biopsy of dysganglionic large bowel. Eur J Pediatr Surg. 1994;4:362–5.

15 Karnovsky MJ, Roots L. A "Direct-Coloring" Thiocholine Method for Cholinesterases. J Histochem Cytochem. 1964;12:219–21.

16 Santos MM, Tannuri U, Coelho MC. Study of acetylcholinesterase activity in rectal suction biopsy for diagnosis of intestinal dysganglionoses: 17-year experience of a single center. Pediatr Surg Int. 2008;24:715–9.

17 Lorijn F De, Kremer LCM, Reitsma JB, et al. Diagnostic Tests in Hirschsprung Disease : A Systematic Review. J Pediatr Gastroenterol Nutr. 2006;42:496–505.

18 Lake BD, Puri P, Nixon HH, et al. Hirschsprung's disease: an appraisal of histochemically demonstrated acetylcholinesterase activity in suction rectal biopsy specimens as an aid to diagnosis. Arch Pathol Lab Med. 1978;102:244–7.

19 Ikawa H, Kim SH, Hendren WH, et al. Acetylcholinesterase and manometry in the diagnosis of the constipated child. Arch Surg (Chicago, Ill 1960). 1986;121:435–8.

20 Croffie JM, Davis MM, Faught PR, et al. At what age is a suction rectal biopsy less likely to

provide adequate tissue for identification of ganglion cells? J Pediatr Gastroenterol Nutr. 2007;44:198–202.
21 Kapur RP. Practical pathology and genetics of Hirschsprung's disease. Semin Pediatr Surg. 2009;18:212–23.
22 Aldridge RT, Campbell PE. Ganglion cell distribution in the normal rectum and anal canal. A basis for the diagnosis of Hirschsprung's disease by anorectal biopsy. J Pediatr Surg. 1968;3:475–90.
23 Moore SW, Johnson G. Acetylcholinesterase in Hirschsprung's disease. Pediatr Surg Int. 2005;21:255–63.
24 Park WH, Choi SO, Kwon KY, et al. Acetylcholinesterase histochemistry of rectal suction biopsies in the diagnosis of Hirschsprung's disease. J Korean Med Sci. 1992;7:353–9.

CHAPTER 3

Anorectal manometry may reduce the number of rectal suction biopsy procedures needed to diagnose Hirschsprung's disease

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SUMMARY

Background

The current most commonly used diagnostic procedure for Hirschsprung's disease (HD) is rectal suction biopsy (RSB), which has its limitations and carries a risk of complications. Anorectal manometry (ARM) is a non-invasive tool with the potential to reduce the number of invasive biopsy procedures. The aim of the study was to evaluate whether anorectal manometry (ARM), which is used to test the rectoanal inhibitory reflex (RAIR), is a safe alternative for reducing the number of invasive rectal suction biopsy (RSB) procedures needed to diagnose Hirschsprung disease (HD).

Methods

Between 2010 and 2017, we prospectively collected the ARM results of 105 patients suspected of having HD. Following the outcome, the patients either underwent additional tests to confirm HD or they were treated conservatively. Primary ARM-based diagnoses were compared with the definitive diagnoses based on the pathology reports and/or clinical follow-ups. Additionally, we analyzed whether modifications to our ARM protocol improved diagnostic accuracy.

Results

The sensitivity of ARM and RSB was comparable (97% versus 97%). The specificity of ARM, performed according to our initial protocol, was significantly lower than that of RSB. After we modified the protocol the difference between the specificity of ARM and RSB was no longer statistically significant (74% versus 84%, respectively, $P = .260$). The negative predictive value of ARM was 100%, while their positive predictive value was significantly lower than that of RSB (56% versus 97%, $P < .001$).

Conclusions

ARM is a viable screening tool for HD and, provided it is performed properly, it can be used to exclude HD with absolute certainty. By contrast, an absent rectoanal inhibitory reflex on ARM should always be followed by an RSB to confirm the diagnosis of HD. Using ARM as the diagnostic of first choice could reduce the number of invasive biopsies.

INTRODUCTION

Constipation is common among infants and newborns.[1] In rare cases constipation may be caused by Hirschsprung's disease (HD), a congenital absence of ganglion cells, aganglionosis, of the enteric nervous system.

Currently, rectal suction biopsy (RSB) is the most commonly used procedure for the diagnosis of HD.[2] However, RSBs in very young patients can be unreliable and 17% of the biopsies need to be repeated due to inconclusive test results.[3] In addition, RSBs are invasive and carry the risk of complications.[4] Taking into account these limitations, in combination with the high prevalence of constipation in the pediatric population, we propose the use of a less invasive tool in order to reduce the number of invasive RSBs.

Anorectal manometry (ARM) is just such a non-invasive tool that carries little or no risks. ARM consists of dilating a rectal balloon and measuring the response in anal sphincter pressure. In healthy individuals, rectal balloon stimulation is followed by a rectoanal contractile reflex (RACR) and a rectoanal inhibitory reflex (RAIR).[5] In patients with HD, however, the RAIR is absent.[6–8] A RAIR found by using ARM thus obviates the need for RSB as HD has virtually been excluded. By contrast, not finding a RAIR might be an indication of HD and warrants a RSB, either to confirm the definitive diagnosis of HD or to discard it. Unfortunately in the past, performing ARMs in very young patients was disputed because of the difficulties encountered in doing so.[2,9] As a consequence, only a small percentage of pediatric surgeons still uses ARM in the diagnosis of HD, while the majority opts for RSB as the diagnostic of first choice.[10,11] This might not be entirely justified, because the value of ARM as a useful screening tool for HD has been demonstrated repeatedly.[9,12–16]

In recent years, modifications to our ARM protocol have helped us to increase its diagnostic accuracy. We hypothesize that with these improvements, ARM could be used to reduce the number of invasive biopsies needed to diagnose HD, and to serve as a complement to RSB in the diagnosis of other causes of constipation in infants and children. Our aim is therefore to evaluate whether ARM performed with our modified protocol is a viable and safe screening tool for HD.

METHODS

Study design

Between 2010 and 2017, we prospectively collected data on 105 patients who were suspected of having HD and who underwent ARM at the Anorectal Physiology Laboratory of the University Medical Center Groningen. The inclusion criteria and indications for performing ARM were delayed meconium passage, distended abdomen, difficult

spontaneous defecation, and/or signs of Hirschsprung's-associated enterocolitis. There were no exclusion criteria. A pediatric surgeon with many years of ARM experience analyzed and interpreted all the measurements blindly and independently from other clinical data. Based on the outcomes of the ARM tests and the patients' clinical condition, patients either underwent additional testing, such as RSB or full-thickness biopsies, or they were treated conservatively with laxatives and rectal washouts. The age at which the biopsies were performed was corrected for the infants' gestational age, whereby a minimal duration of 38 weeks was considered normal. The medical ethics committee of University Medical Center Groningen approved the study.

Anorectal manometry procedure

Measuring equipment

We recorded and analyzed the data with solar gastrointestinal high resolution manometry equipment (Laborie/Medical Measurement Systems, Enschede, the Netherlands, version 9.30). We used a Laborie (Unisensor) K12959 catheter with an outer diameter of 12F, circumferential pressure sensors taking a reading every 8 mm over a total length of 5.6 cm, and a microtip sensor within a small, non-latex balloon attached to the tip of the catheter to inflate it and to register the pressure inside the balloon.

Anorectal manometry protocol

A few minutes prior to insertion the catheter was warmed-up in water at body temperature, after which a small amount of inert gel was applied to the balloon. The level to which the catheter was inserted depended on the age of the patient; preferably it was inserted until the last pressure sensor was visible at the edge of the anal canal. Once it was in place, the catheter was fixed to the patient's buttocks with tape. After insertion a few minutes were allowed for the anal sphincter pressure to return to base value. At intervals of at least thirty seconds the rectoanal reflexes were measured by inflating the rectal balloon with increasing volumes of air that were rapidly injected and ejected after one second.

During the course of the study we modified the ARM protocol significantly by adjusting the maximum dilatation volumes of the rectal balloon. In the initial protocol, which was used from 2010 to 2014, the balloon was inflated with small steps of, for example 1, 2, or 3 mL at a time, until the dilatation volume was considered maximal for the age of the patient. In the modified protocol, which we used from 2014 to 2017, the balloon was inflated with steps of, for example, 1, 3, 5, or 8 mL, until we observed either the RACR or the RAIR. Even though our safety protocol mentioned that inflation should only be increased until resistance to inflating the balloon increased or the patient showed signs of discomfort, none of our patients reached this level.

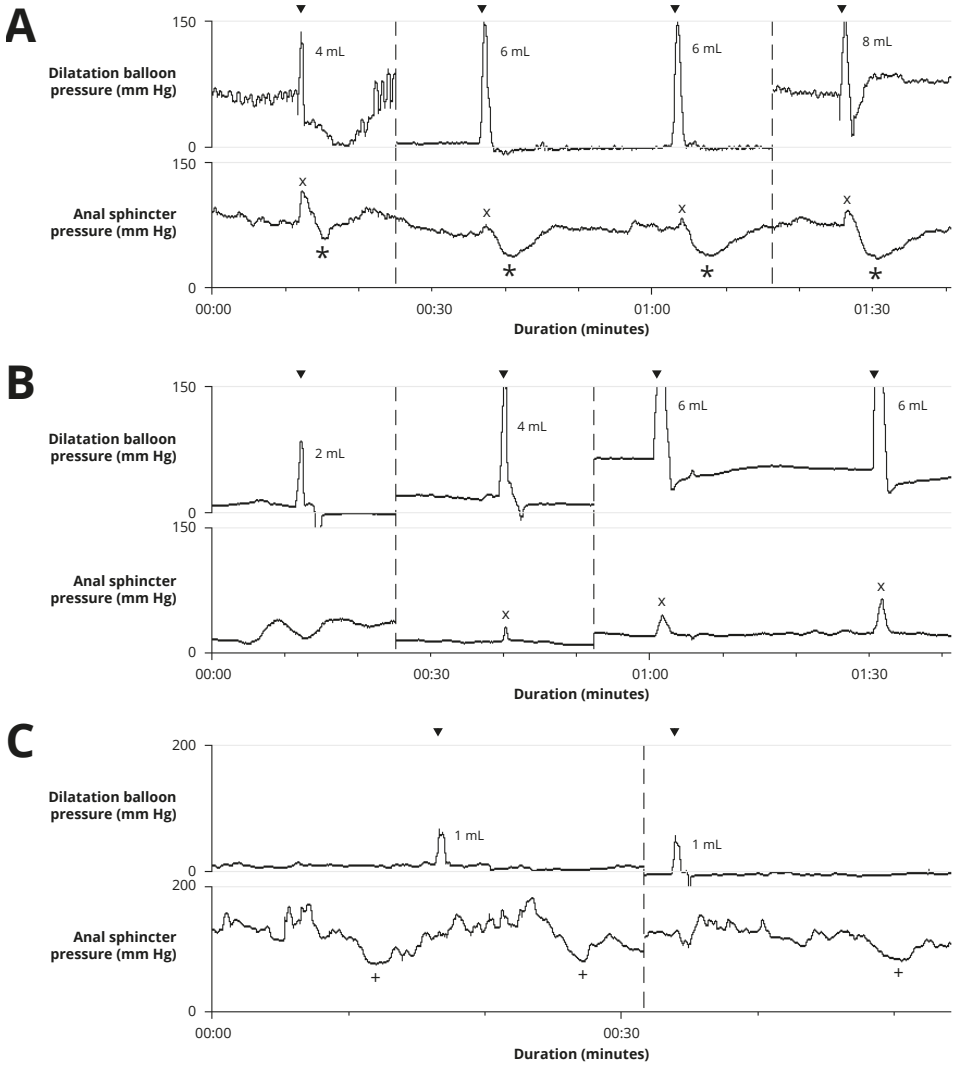

Figure 1

Rectoanal anal reflexes measured by anorectal manometry. Arrowheads denote the moment of dilatation, crosses denote the rectoanal contractile reflex, asterisks denote the rectoanal inhibitory reflex, and plusses denote spontaneous relaxations.

A: Patient without Hirschsprung's disease with a functional rectoanal contractile reflex and rectoanal inhibitory reflex. Note that the rectoanal inhibitory reflex becomes deeper and longer with increasing balloon dilatation.

B: Patient with Hirschsprung's disease with a functional rectoanal contractile reflex but an absent rectoanal inhibitory reflex. Note that in this patient the rectoanal contractile reflex was only elicited after a minimal dilatation of 4 mL.

C: Patient with Hirschsprung's disease with spontaneous relaxations of the anal sphincter, which should not be interpreted as a rectoanal inhibitory reflex. Note that the moment of dilatation and the relaxation do not coincide.

Anorectal manometry interpretation

The RACR was defined as a rapid and temporary increase of anal sphincter pressure of at least 10 mm Hg directly following balloon dilatation. The anal pressure difference had to be significantly more pronounced with increasing rectal dilatation (Figure 1B). A functioning RAIR was defined as a decrease in anal sphincter pressure of at least 20 mm Hg following balloon dilatation. As depicted in Figure 1A, the difference in anal pressure has to be significantly more pronounced with increasing rectal dilatation. We did not consider spontaneous relaxations of the anal sphincter, without direct preceding rectal dilatations, to be rectoanal inhibiting relaxations (Figure 1C). We defined ARM as positive for HD if the RAIR was absent. ARM was defined as inconclusive if there was no clear relaxation of the anal sphincter, that is a threshold of 20 mm Hg relaxation was not reached, or if the morphology of the RAIR was abnormal. Lastly, ARM was defined as negative for HD if the RAIR was present, with increasing relaxation of the anal canal with increasing rectal dilatations.

Rectal suction biopsy procedure

The RSB procedure we used consisted of extracting specimens at three levels, that is 3, 4.5, and 6 cm above the anal verge. Subsequently, the specimens were stained with hematoxylin and eosin, nicotinamide adenine dinucleotide enzyme histochemistry, and acetylcholinesterase histochemistry. We had to exclude ten RSBs due to insufficient tissue for the diagnosis of HD. The remaining RSBs were classified as positive for HD, that is no ganglion cells and/or increased nerve fiber proliferation, inconclusive for Hirschsprung, that is no ganglion cells and little or no nerve fiber proliferation, or negative for HD, that is ganglion cells and little or no increased nerve fiber proliferation.

Data analysis

We compared the outcomes of ARM with the final diagnoses based on the pathology reports and/or clinical follow-ups. On the basis of the final diagnoses, the ARM test results were classified as true positive, false positive, true negative, false negative, or inconclusive. Using these criteria, we determined diagnostic aspects such as sensitivity, specificity, positive predictive value, and negative predictive value for ARMs. The same was done for the RSBs. By doing so, we were able to compare the diagnostic aspects of ARMs and RSBs.

In order to analyze the outcomes of ARM at different ages, we divided the patients into three equally sized groups on the basis of their age percentiles: 14 to 65, 66 to 167, and 168 to 5532 days of age (corrected for gestational age).

We modified the ARM protocol on the basis of our experience. To test the effect of

these modifications, we compared the diagnostic aspects of ARMs performed according to the initial protocol (n = 64) to those performed according to the modified protocol (n = 41).

Statistical analysis

Data were analyzed with IBM SPSS Statistics 23 for Windows (IBM Corporation, Armonk, NY). We reported continuous values as medians with range. Statistical tests were limited to Pearson's chi-squared test and the Mann-Whitney tests. Sensitivity and specificity values were defined as the proportion of positives and negatives correctly identified as such. Positive and negative predictive values were defined as the proportions of positive and negative results that were defined as true positive and true negative test results, respectively. Two-sided *P* values of less than .050 were considered statistically significant.

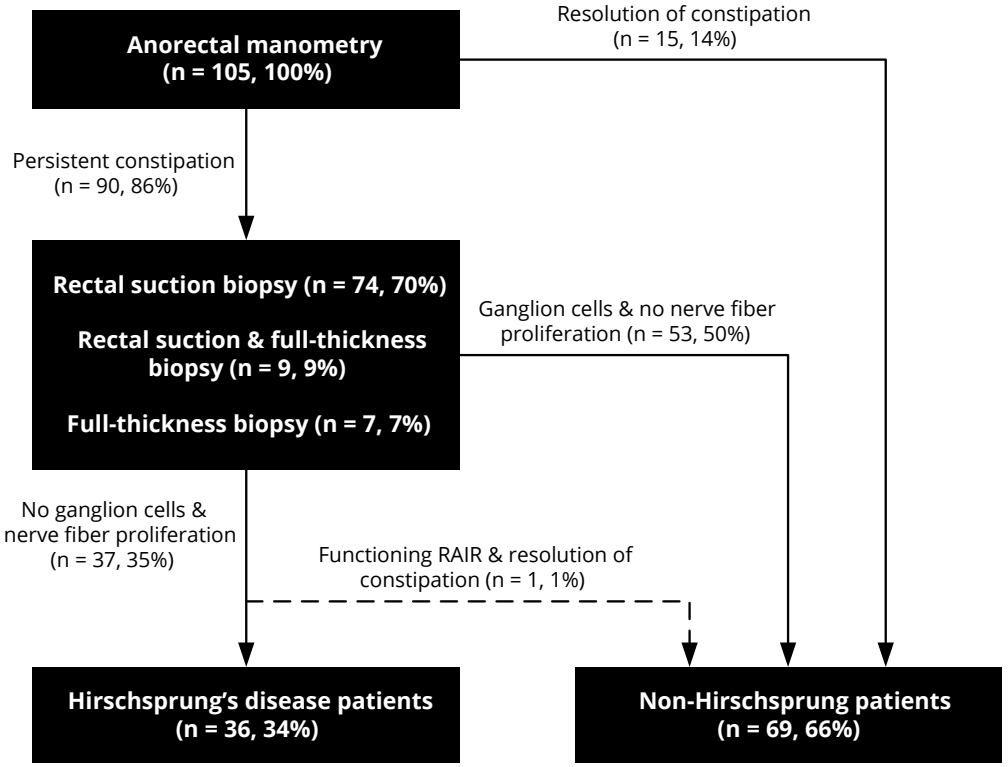

Figure 2

Study flow diagram. Note that one patient was initially diagnosed with Hirschsprung's disease following the results of rectal suction biopsy, a diagnosis which was later contradicted on the basis of a functioning rectoanal inhibitory reflex and a complete resolution of constipation.

RESULTS

Patient characteristics

A total of 105 patients suspected of having HD and who had undergone ARM were included. The majority of patients was male (63%, n = 66). Patients' median gestational age was 39 weeks (range 26 to 42 weeks). The first presenting symptom was a delayed meconium passage in 41% (n = 43) of the patients, chronic constipation in 55% (n = 58), sigmoid volvulus in 2% (n = 2), and an intestinal perforation in 2% (n = 2). Following the ARM, one or more RSBs were performed in 79% of the patients (n = 83), while 15% (n = 16) required a full-thickness biopsy to arrive at the final diagnosis (Figure 2). The remaining 15 patients (14%) did not require a biopsy because at follow-up constipation had resolved completely or near-completely. Ultimately, we diagnosed 34% (n = 36) of the patients with HD (Figure 2).

Anorectal manometry outcomes

Patients' age at the time of ARM ranged from -14 days (preterm birth, corrected for gestational age) to 5532 days, that is, 15 years, with a median age of 114 days. Over the entire study period, we found that the sensitivity of ARM was 97%, while its specificity was 42% (Table 1). A positive ARM result had a positive predictive value of 56% for eventual HD. Notably, a negative ARM result excluded HD with absolute certainty, the negative predictive value being 100%.

We found no significant differences in diagnostic accuracy of ARM among the three age groups investigated (Table 2). The sensitivity ranged from 94% to 100% (P = .526) and the specificity ranged from 35% to 48% (P = .580).

Rectal suction biopsy outcomes

We analyzed a total of 83 RSBs performed in 77 patients. The median age at the time of RSB was 83 days, with a minimum of -14 days (preterm birth, corrected for gestational age) and a maximum of 1522 days, that is 4 years. Overall, the sensitivity of the RSBs was 97% and specificity was 84% (Table 1). Moreover, RSBs had a positive predictive value of 97% and a negative predictive value of 100%.

Comparison of anorectal manometry and rectal suction biopsy

Additionally, we compared the outcomes of the results of 105 ARMs with the results of 83 RSBs and found no significant difference in sensitivity between the two tests (Table 1). The specificity of RSBs, however, we found to be significantly higher than that of ARMs (84% versus 42%, P < .001). Moreover, the positive predictive value of RSBs was

Table 1
Comparison of anorectal manometry and rectal suction biopsy

Group	Outcome	Anorectal manometry (Total group, n = 105)	Rectal suction biopsy (n = 83)	*P* value
HD patients	True positive (n)	35/36 (97%[a])	33/34 (97%[a])	.967
	Inconclusive (n)	1/36 (3%)	1/34 (3%)	.967
	False negative (n)	0/36 (0%)	0/34 (0%)	
Non-HD patients	True negative (n)	29/69 (42%[b])	41/49 (84%[b])	< .001
	Inconclusive (n)	13/69 (19%)	7/49 (14%)	.516
	False positive (n)	27/69 (39%)	1/49 (2%)	< .001
Group	Outcome	Anorectal manometry (Modified protocol, n = 41)	Rectal suction biopsy (n = 83)	*P* value
HD patients	True positive (n)	7/7 (100%[a])	33/34 (97%[a])	.646
	Inconclusive (n)	0/7 (0%)	1/34 (3%)	.646
	False negative (n)	0/7 (0%)	0/34 (0%)	
Non-HD patients	True negative (n)	25/34 (74%[b])	41/49 (84%[b])	.260
	Inconclusive (n)	3/34 (9%)	7/49 (14%)	.452
	False positive (n)	6/34 (18%)	1/49 (2%)	*.012*

[a] Sensitivity, [b] Specificity

significantly higher than that of ARMs (97% versus 56%, $P < .001$). The negative predictive value of both tests was 100%.

One patient had a false positive RSB result. While the biopsies taken at 4.5 and 6 cm from the anal verge showed normal nerve innervation, the biopsy taken at 3 cm showed complete absence of ganglion cells and a proliferation of AChE positive nerve fibers, compatible with short segment HD. The ARM performed in this patient, however, showed a functioning RAIR at a dilatation of 5 mL, contradicting the diagnosis of HD. Following a conservative treatment with rectal washouts and laxatives, constipation had completely disappeared at follow-up within one year.

Finally, following a RSB, one patient had rectal blood loss and required hospitalization and surgical hemostasis. No complications occurred during any of the ARM tests.

Comparison of anorectal manometry protocols

Next, we compared the initial ARM protocol (n = 64) with the modified ARM protocol (n = 41) (Table 3). One of the main differences between the two protocols was that in the modified protocol the balloon was inflated until either a RACR or a RAIR was elicited. This method meant that the maximal volume used for dilatation was significantly higher in the modified protocol than in the initial protocol (median 9.5 mL versus 3 mL, $P < .001$). Using this modified protocol we induced a RACR in 78% of the patients, whereas in the initial protocol this was 13% ($P < .001$). Modification of the protocol also resulted in an increased prevalence of the RAIR (68% versus 17%, $P < .001$).

The use of higher dilatation volumes in the modified protocol drastically increased specificity in comparison to the initial protocol (74% versus 11%, $P < .001$, Table 3). The

Table 2
Diagnostic accuracy of anorectal manometry at different ages

Group	Outcome	Ages of patients at time of anorectal manometry			*P* value
		-14 to 65 days (n = 35)	66 to 167 days (n = 35)	168 to 5532 days (n = 35)	
HD patients	True positive (n)	18/18 (100[a])	15/16 (94%[a])	2/2 (100%[a])	.526
	Inconclusive (n)	0/18 (0%)	1/16 (6%)	0/2 (0%)	.526
	False negative (n)	0/18 (0%)	0/16 (0%)	0/2 (0%)	
Non-HD patients	True negative (n)	6/17 (35%[b])	7/19 (37%[b])	16/33 (48%[b])	.580
	Inconclusive (n)	4/17 (24%)	4/19 (21%)	5/33 (15%)	.741
	False positive (n)	7/17 (41%)	8/19 (42%)	12/33 (36%)	.902

[a] Sensitivity, [b] Specificity

other diagnostic aspects, such as sensitivity, positive predictive value, and negative predictive value, were not significantly different between the two protocols (Table 3).

Lastly, we compared the outcomes of the modified ARM protocol (n = 41) with the results of RSBs (n = 83, Table 1). After modification, the specificity of the ARMs increased and was no longer significantly different from the RSBs (74% versus 84%, *P* = .260). Moreover, there were no significant differences in sensitivity between the modified ARM protocol and the RSBs (100% versus 97%, *P* = .646).

DISCUSSION

While ARM is widely accepted as a diagnostic tool in older children and adults suspected of having HD, its use in newborns is disputed because of the possibility of finding false negatives and false positives.[2,9] To some degree, the results of our study contradicted this fear, as our tests showed no false negatives. In other words, a functioning RAIR found by ARM excludes HD with certainty and obviates the need for a RSB.

In contrast to having no false negative test results, our results did indeed show that ARM carried the risk of false positive test results in the diagnosis of HD. We offer various

Table 3
Comparison of anorectal manometry protocols

	Initial protocol No. (%)	Modified protocol No. (%)	*P* value
Overall	64 (100)	41 (100)	
Rectoanal reflex tests			
Functioning RAIR	11/64 (17)	28/41 (68)	< .001
RAIR stimulation threshold (mL)*	2 (1 – 15)	5 (1 – 15)	.005
Functioning RACR	8/64 (13)	32/41 (78)	< .001
RACR stimulation threshold (mL)*	4.5 (2 – 10)	4 (1 – 50)	.805
Maximum balloon dilatation (mL)*	3 (1 – 30)	9.5 (4 – 60)	< .001
Diagnostic accuracy measures			
Sensitivity	28/29 (97)	7/7 (100)	.618
Specificity	4/35 (11)	25/34 (74)	< .001
Positive predictive value	28/49 (57)	7/13 (54)	.831
Negative predictive value	4/4 (100)	25/25 (100)	

RACR, rectoanal contractile reflex; RAIR, rectoanal inhibitory reflex;
* Median (range)

possible explanations for the lower specificity in ARMs. First, we learned from our clinical observations that insufficient inflation of the rectal balloon might not stimulate the rectal wall sufficiently, thus failing to elicit a response to anal sphincter pressure. This could explain the false positive test results found in patients with increased rectal volumes due to severe outlet obstructions. Second, some of the inconclusive and false positive ARM results may be the result of our strict criteria for the interpretation of ARM. As an example, ARM was only considered negative for HD if the RAIR was present, and when the relaxation of the anal canal increased with increasing rectal dilatations. While these strict criteria have resulted in a high sensitivity and a high negative predictive value, they may have also resulted in a lower specificity and a reduced positive predictive value. Last, inability to elicit the RAIR could also be the result of a delay in the development of this reflex. The literature does not agree on this issue. One study showed that the RAIR does indeed develop after birth,[17] while another study found that the RAIR is already present at birth, even in preterm-born infants.[18] Further research is required to determine whether development of the RAIR in particular or development of the physiology of the anal canal in general, plays a role in constipation in newborns. The false positive ARM results do, however, mean that at all times it remains necessary to perform a RSB in case no RAIR was found by ARM.

While RSB is currently the most commonly used tool for diagnosing HD,[2] it too might have its shortcomings. First, RSBs have a significantly lower sensitivity in patients younger than 38 days in comparison to older patients.[3] Moreover, RSBs also seem to carry the small risk of false HD diagnoses, as demonstrated by the false positive RSB outcome in our current study that was later disputed by the ARM test result and clinical follow-up. Lastly, while a RSB is generally considered safe, the risk of complications remain due to its invasive nature.[4] We too had one serious complication following RSB, which had to be treated surgically. Aside from this complication, we had to exclude of the biopsies because of insufficient material, after which the biopsies had to be repeated. These negative experiences with RSBs are corroborated by the reports of others.[19,20] These limitations, we believe, can be overcome partially by utilizing the advantages of ARM–the main advantage being that it is non-invasive and therefore carries no risks of complications.

The primary limitation of our study was that not all patients underwent a biopsy to confirm or exclude the diagnosis of HD. In patients with HD, all the diagnoses were confirmed by RSBs and in the majority of cases the diagnosis was confirmed by post-operative pathological inspection of the intestinal resection. Not every patient in whom HD had been excluded, however, underwent a RSB procedure. As a consequence, ARM test results may have been wrongly labeled as true negative, thus overestimating diagnostic

accuracy. We do believe, however, that if the diagnosis of HD had been missed at a young age, constipation would most likely have persisted and the diagnosis would have been reconsidered at a later age. Recently, we experienced such cases in two patients who were eventually diagnosed with HD at 18 and 14 years of age.[21] Another limitation of this study may be the setting, namely a tertiary referral center with a relatively high prevalence of HD (up to 34% in this study). This limitation might have partially biased the predictive values we found, as these are affected by the disease prevalence.[22]

Lessons learned using anorectal manometry to exclude Hirschsprung's disease

As mentioned before, HD is excluded once ARM reveals that RAIR is activated upon rectal dilatation, which is a safe and non-invasive procedure. However, because the rectal volumes differ between patients it is difficult to standardize the volumes required for successfully eliciting the RAIR. Lack of such standardization has raised doubts about the reliability of ARM, especially in terms of reproducibility. Unfortunately, many medical centers have therefore opted for RSB as the first-choice diagnostic,[10,11] which seems to be technically easier to perform than ARM. However, if the benefit for the patient is taken into account, that is the non-invasive nature of ARM, and the high specificity and sensitivity described before,[2] and also in this study, we think that ARM should be considered in every center's HD workup protocol.

During the study we learned several valuable lessons that helped us improve the diagnostic accuracy of ARM. First, we found that it is important to accurately register the precise moment the balloon is inflated (Figure 1C). Such accurate registration is necessary to determine whether a difference in sphincter pressure is caused by random relaxation or whether it occurred as result of a rectal dilatation. Second, we learned that in case of a functional RAIR, relaxation following balloon dilation should become deeper and longer when the balloon is increasingly inflated (Figure 1A). Continuing to inflate the balloon, even after having found a functional RAIR, further reduces the risk of a false negative test result. The last and most important lesson we learned is that it is important to keep on inflating the balloon until a RACR is elicited (Figure 1B). One of the reasons for a false positive test result is inadequate stimulation of the rectal wall because, in some constipated children and newborns, the rectal volume may be larger than is to be expected considering their age. In such patients dilation of 5 mL will be insufficient to stimulate the rectal wall. In the majority of patients a dilatation with at least 10 mL was necessary to elicit the RAIR.

Conclusion

ARM is a viable screening tool for excluding HD, provided the correct technical

improvements are made. Importantly, a functioning RAIR found by ARM obviates the need for a RSB, because HD has virtually been excluded. By contrast, no functioning RAIR warrants a RSB to confirm or exclude the diagnosis of HD. By using ARM as the diagnostic of first choice the number of invasive biopsies, and therefore the risk of complications, can be reduced. This study can form the starting point towards a standardized method for the measuring and appraisal of anorectal reflexes in HD.

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REFERENCES

1 Mugie SM, Benninga MA, Lorenzo C Di. Epidemiology of constipation in children and adults: A systematic review. Best Pract Res Clin Gastroenterol. 2011;25:3–18.

2 Lorijn F De, Kremer LCM, Reitsma JB, et al. Diagnostic Tests in Hirschsprung Disease : A Systematic Review. J Pediatr Gastroenterol Nutr. 2006;42:496–505.

3 Meinds RJ, Kuiper GA, Parry K, et al. Infant's Age Influences the Accuracy of Rectal Suction Biopsies for Diagnosing of Hirschsprung's Disease. Clin Gastroenterol Hepatol. 2015;13:1801–7.

4 Friedmacher F, Puri P. Rectal suction biopsy for the diagnosis of Hirschsprung's disease: a systematic review of diagnostic accuracy and complications. Pediatr Surg Int. 2015;31:821–30.

5 Bharucha AE. Pelvic floor: anatomy and function. Neurogastroenterol Motil. 2006;18:507–19.

6 Schnaufer L, Talbert JL, Haller JA, et al. Differential sphincteric studies in the diagnosis of ano-rectal disorders of childhood. J Pediatr Surg. 1967;2:538–43.

7 Lawson JO, Nixon HH. Anal canal pressures in the diagnosis of Hirschsprung's disease. J Pediatr Surg. 1967;2:544–52.

8 Scharli AF. Pathophysiology of Classical Hirschsprung's disease. In: Holschneider AM, Puri P, editors. Hirschsprung's Disease and Allied Disorders. Frankfurt, Germany: Springer; 2000. p. 109–25.

9 Iwai N, Yanagihara J, Tokiwa K, et al. Reliability of anorectal manometry in the diagnosis of Hirschsprung's disease. Z Kinderchir. 1988;43:405–7.

10 Bradnock TJ, Walker GM. Evolution in the management of Hirschsprung's disease in the UK and Ireland: A national survey of practice revisited. Ann R Coll Surg Engl. 2011;93:34–8.

11 Zani A, Eaton S, Morini F, et al. European Paediatric Surgeons' Association Survey on the Management of Hirschsprung Disease. Eur J Pediatr Surg. 2016;27:96–101.

12 Emir H, Akman M, Sarimurat N, et al. Anorectal manometry during the neonatal period: its specificity in the diagnosis of Hirschsprung's disease. Eur J Pediatr Surg. 1999;9:101–3.

13 Huang Y, Zheng S, Xiao X. Preliminary evaluation of anorectal manometry in diagnosing Hirschsprung's disease in neonates. Pediatr Surg Int. 2009;25:41–5.

14 Noviello C, Cobellis G, Papparella A, et al. Role of anorectal manometry in children with severe constipation. Color Dis. 2009;11:480–4.

15 Noviello C, Cobellis G, Romano M, et al. Diagnosis of Hirschsprung's Disease: an age-related approach in children below or above one year. Colorectal Dis. 2010;12:1044–8.

16 Lorijn F De, Reitsma JB, Voskuijl WP, et al. Diagnosis of Hirschsprung's disease: a prospective, comparative accuracy study of common tests. J Pediatr. 2005;146:787–92.

17 Howard ER, Nixon HH. Internal anal sphincter. Observations on development and mechanism of inhibitory responses in premature infants and children with Hirschprung's disease. Arch Dis Child. 1968;43:569–78.

18 de Lorijn F, Omari TI, Kok JH, et al. Maturation of the rectoanal inhibitory reflex in very premature infants. J Pediatr. 2003;143:630–3.

19 Hall NJ, Kufeji D, Keshtgar A. Out with the old and in with the new: a comparison of rectal suction biopsies with traditional and modern biopsy forceps. J Pediatr Surg. 2009;44:395–8.

20 Hayes CE, Kawatu D, Mangray S, et al. Rectal Suction Biopsy to Exclude the Diagnosis of Hirschsprung's Disease. J Pediatr Gastroenterol Nutr. 2012;55:1.

21 Meinds RJ, van der Doef HPJ, Bodewes FAJA, et al. Solitary Rectal Ulcer Syndrome as a Sign of Unrecognized Hirschsprung Disease. J Pediatr. 2016;177:321–321.e1.
22 Baldessarini RJ, Finkelstein S, Arana GW. The Predictive Power of Diagnostic-Tests and the Effect of Prevalence of Illness. Arch Gen Psychiatry. 1983;40:2–6.

CHAPTER 4

Immaturity of the rectoanal inhibitory reflex as a cause of severe constipation in newborns

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Submitted

SUMMARY

Background

The rectoanal inhibitory reflex (RAIR) plays an important role in the defecation process and is responsible for the relaxation of the internal anal sphincter upon rectal stimulation. On the basis of literature and our clinical experience, we hypothesize that the RAIR may not always have reached full maturity at birth. In addition, we hypothesize that immaturity of the RAIR may play a role in symptoms of constipation in a subgroup of newborns.

Methods

In the period of 2011 to 2017 we prospectively gathered data on newborns who presented themselves with severe constipation to our tertiary center, who had an absent or immature RAIR, as measured with anorectal manometry (ARM), and who underwent at least one follow-up ARM measurement. Patients with an organic cause for constipation were excluded (*e.g.* Hirschsprung's disease).

Results

A total of eight patients were included, all males. None of these patients had a fully matured RAIR on the initial measurement, all patients required high dose laxatives, and six out of eight patients required daily rectal washouts. At follow-up measurement, seven out of eight patients had developed a fully matured RAIR, seven patients' parents reported decreased severity of constipation complaints, whereas only two patients still required rectal washouts.

Conclusions

Severe constipation in newborn infants can be caused by a dysfunctional and immature RAIR, which may be able to further mature with aging. Correspondingly, symptoms of constipation decrease as the RAIR matures. During this period sufficient conservative treatment with laxatives and rectal washouts may prevent severe dilatation of the rectum.

INTRODUCTION

Constipation is a commonly reported symptom in infants, with an estimated prevalence of 10.7-13.7% throughout the first year of life.[1] Acute signs of constipation in infants are a delayed passage of meconium, vomiting, diarrhea, or severe abdominal distension, whereas more chronic signs are weight loss, or failure to thrive.[2] In this young group of patients, anorectal manometry (ARM) provides a simple and safe solution to test the functioning of the anorectal physiology, including the presence of the rectoanal inhibitory reflex (RAIR).

The RAIR is the relaxation of the internal anal sphincter following rapid distention of the rectum which leads to a decrease in anal pressure.[3] Failure of the internal anal sphincter to relax in response to rectal distension is seen in Hirschsprung's disease (congenital aganglionosis),[4–6] a disease associated with severe constipation. The absence of ganglion cells and changes in neurotransmitter release in Hirschsprung's disease could be an indication that these parts of the enteric nervous system are vital for the RAIR to function.[7] Aside from structural changes in the enteric nervous system seen in Hirschsprung's disease, there have also been reports of immaturity of the enteric nervous system at birth.[8,9] The physiological consequences of an immature enteric nervous system are not completely clear, especially if the functioning of the RAIR is taken into account. Since the functioning of RAIR requires well-functioning of the enteric nervous system, it seems logic that, along with the maturation of the enteric nervous system, the functioning of the RAIR can also mature.

Immaturity and subsequent maturation of the RAIR after birth have been studied before, albeit with inconsistent outcomes.[10–13] One of these studies demonstrated RAIR could indeed mature after birth,[10] whereas more recent studies concluded the RAIR to be fully matured at birth even in premature infants.[11–13] These latter studies, however, primarily involved healthy newborns without symptoms of constipation that could indicate a delayed maturation of the RAIR. It therefore remains unclear whether the RAIR is fully matured at birth in every infant, especially in those with severe constipation.

Basing ourselves on the aforementioned, we hypothesize that an immature RAIR might play a role in constipation in a subgroup of infants. Correspondingly, development and maturation of this reflex should alleviate these symptoms. The aim of this study was to investigate the development of the RAIR and to evaluate its effect on symptoms of constipation.

METHODS

Study design

In the period of 2011 to 2017 we prospectively gathered data on patients who presented themselves to our tertiary center with severe constipation and who underwent ARM at the Anorectal Physiology Laboratory of the University Medical Center Groningen. The inclusion criteria were absence or malfunctioning of the RAIR observed during the initial ARM and at least one follow-up ARM measurement. The only exclusion criterion was the presence of an organic cause for the constipation, for example Hirschsprung's disease or congenital anorectal malformation.

Additionally, we collected data on symptoms of constipation and the usage of therapy for constipation (that is, laxatives and need for rectal washouts) from outpatient clinic reports. Changes in symptoms of constipation, such as improvement or deterioration, were based on reports from parents and physical examination.

Anorectal manometry procedure

Measuring equipment

We recorded and analyzed the data with solar gastrointestinal high resolution manometry equipment (Laborie/Medical Measurement Systems, Enschede, the Netherlands, version 9.30). We used a Laborie (Unisensor) K12959 catheter with an outer diameter of 12F, circumferential pressure sensors taking a reading every 8 mm over a total length of 5.6 cm, and a microtip sensor within a small, non-latex balloon attached to the tip of the catheter to inflate it and to register the pressure inside the balloon.

Anorectal manometry protocol

A few minutes prior to insertion, the catheter was warmed-up in water at body temperature, after which a small amount of inert gel was applied to the balloon. The level to which the catheter was inserted depended on the age of the patient; preferably with two measuring sensors located in the rectum. Once it was in place, the catheter was fixed to the patient's buttocks with tape. After the insertion, a few minutes of rest were given for the anal sphincter pressure to return to base value. At intervals of at least thirty seconds the rectoanal reflexes were evoked by inflating the rectal balloon with increasing volumes of air that were rapidly injected and rejected after approximately one second.

Anorectal manometry interpretation

The RAIR was defined as fully matured when there was a decrease in anal sphincter pressure of at least 20 mm Hg following balloon dilatation. The difference in anal

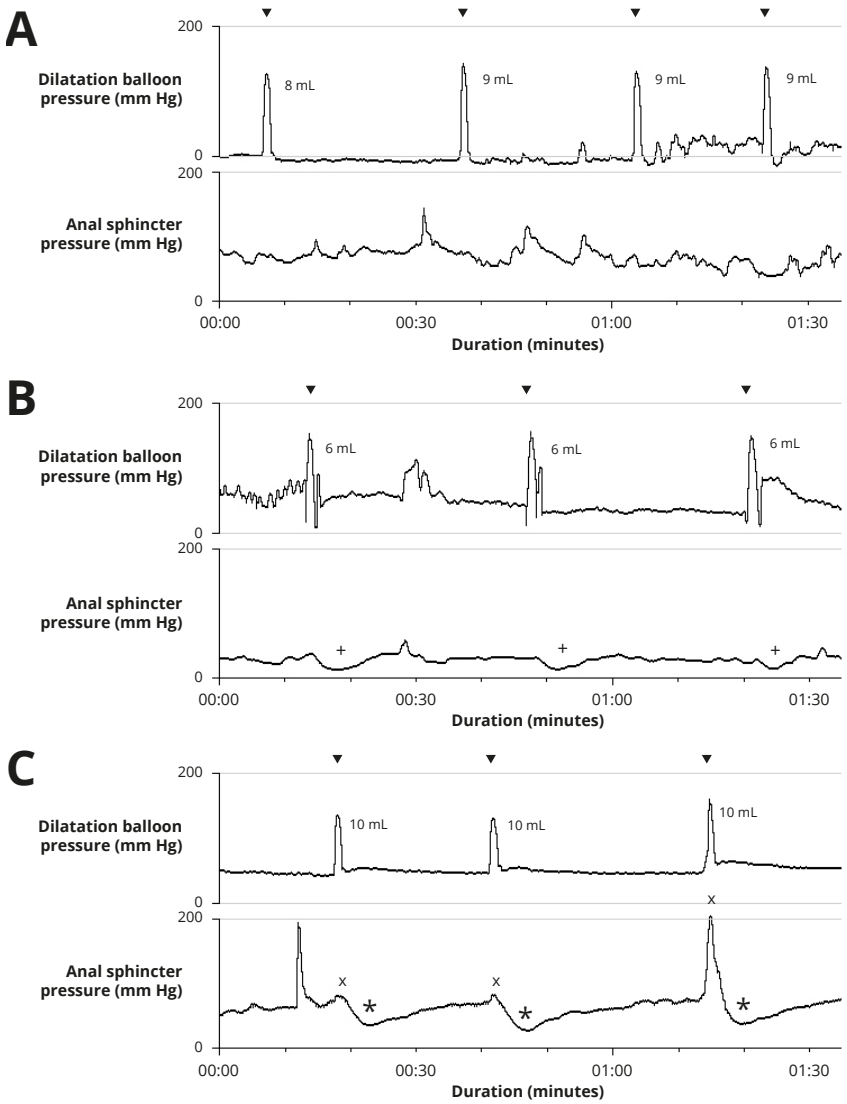

Figure 1

Rectoanal inhibitory reflexes measured by anorectal manometry in three separate patients at various ages. Arrowheads denote the moment of dilatation, plusses denote spontaneous relaxations, and asterisks denote the rectoanal inhibitory reflex.

A: Measurement at 154 days old, showing no response in anal sphincter pressure following rectal stimulation (that is absent rectoanal inhibitory reflex).

B: Measurement at 23 days old, showing a limited response in anal sphincter pressure following rectal stimulation, yet no complete relaxation of the anal sphincter (that is immature rectoanal inhibitory reflex).

C: Measurement at 708 days old, showing an adequate response in anal sphincter pressure following rectal stimulation (that is fully matured rectoanal inhibitory reflex).

pressure had to be significantly more pronounced with increasing rectal dilatation. The RAIR was defined as absent if there was no decrease in anal sphincter pressure following balloon dilation. The RAIR was defined as immature if there was no clear relaxation of the anal sphincter, that is a threshold of 20 mm Hg relaxation was not reached, or if the morphology of the RAIR was abnormal, that is no quick anal relaxation followed by a slow return to the baseline pressure.

RESULTS

Patients characteristic

A total of eight patients met the criteria for inclusion (Table 1). All patients were males. Two of the patients were born prematurely, namely at 28 and 35 weeks, while the rest was born at full term (median gestational age 39 weeks). Six patients produced meconium within 24 hours following birth, one patient between 24 and 48 hours, and one patient ultimately required an enema to produce meconium after failing to do so in the first 48 hours. Following their meconium production, all but one patient experienced persistent severe constipation complaints from birth, which was the reason for their referral to our tertiary center. The last patient initially experienced no complaints but developed severe constipation at the age of 8 weeks old. An organic cause for the constipation complaints was excluded in all patients by rectal biopsy (to exclude Hirschsprung's disease) and thorough physical examination (to exclude congenital anorectal malformation).

Initial anorectal manometry

The initial ARM was performed at a median age of 143 days old, with a minimum of 1 day and maximum 330 days (corrected for gestational age). At time of the initial ARM,

Table 1
Patient characteristics

	No. (%)
Included patients	8 (100)
Boys	8 (100)
Gestational age (weeks)*	39 (28 – 41)
Meconium passage	
< 24 hours	6 (75)
24 - 48 hours	1 (13)
> 48 hours	1 (13)
Age at initial ARM (days)*	143 (1 – 330)
Age at follow-up ARM (days)*	583 (229 – 1275)

* Median (minimum – maximum)

Tabel 2
Case descriptions

Case no.	GA (weeks)	Sex	Age at initial ARM (days)	Initial ARM	Clinical presentation	Age at follow-up ARM (days)	Follow-up ARM	Clinical follow-up
1	39	M	330	Absent RAIR	Chronic constipation since birth, multiple hospital admissions despite laxatives, abdominal distension	618	Functional RAIR	Persistent constipation requiring daily rectal washouts. Minimal improvement of complaints.
2	28	M	1	Immature RAIR	Chronic constipation since birth, manageable with daily rectal washouts and laxatives	708	Functional RAIR	Spontaneous defecation with laxatives, no more need for rectal washouts.
3	39	M	132	Absent RAIR	Chronic constipation since birth, manageable with daily rectal washouts and laxatives	518	Functional RAIR	Spontaneous defecation with laxatives, no more need for rectal washouts.
4	38	M	23	Immature RAIR	Chronic constipation since birth with abdominal distension	548	Functional RAIR	Spontaneous defecation with laxatives, no more need for rectal washouts.
5	35	M	49	Absent RAIR	Chronic constipation since birth, manageable with rectal washouts and laxatives	386	Functional RAIR	Spontaneous defecation with laxatives, no more need for rectal washouts.
6	41	M	167	Immature RAIR	Mild constipation and an anal fissure	229	Immature RAIR	Mild improvement of constipation with laxatives
7	39	M	175	Absent RAIR	Chronic constipation since birth, manageable with rectal washouts and laxatives	733	Functional RAIR	Mild improvement of constipation, manageable with rectal washouts and laxatives.
8	39	M	154	Absent RAIR	Mild constipation complaints and perianal fistula	1275	Functional RAIR	Spontaneous defecation with laxatives, overall improvement of complaints

Abbreviations: ARM, anorectal manometry; GA, gestational age; RAIR, rectoanal inhibitory reflex.

all patients required laxatives and the majority required daily rectal washouts (six out of eight patients) as treatment for their constipation complaints (Table 2). None of the eight patients had a fully matured RAIR during the initial ARM (Table 2). Five patients had an absent RAIR (Figure 1A), while the remaining three patients showed a limited response in anal sphincter pressure following rectal dilatation, but no complete relaxation, indicative of an immature RAIR (Figure 1B).

Follow-up anorectal manometry

The follow-up ARM was performed at a median follow-up of 583 days, with a minimum of 229 days and a maximum of 1275 days. The follow-up ARM showed that seven of the eight patients had a functioning, fully matured RAIR (Figure 1C). The remaining patient showed a limited decrease in anal sphincter pressure following rectal stimulation, yet no complete relaxation, i.e. an immature RAIR (Figure 1B). At follow-up, seven out of eight patients' parents reported improvement of feeding and constipation complaints. Still, all patients used laxatives, whereas only two out of eight patients required rectal washouts, albeit in a lower frequency than initially (Table 2).

Case illustration

As an illustration of the maturation of the RAIR, Figure 2 shows repeated ARM measurements in an individual patient. In the first measurement at 175 days of age the

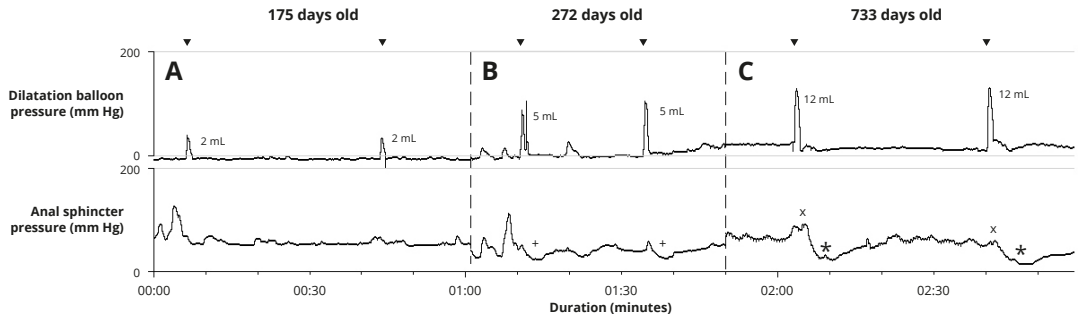

Figure 2

Multiple anorectal manometry measurements showing the maturing of the rectoanal inhibitory reflex in an individual patient. Arrowheads denote the moment of dilatation, plusses denote spontaneous relaxations, and asterisks denote the rectoanal inhibitory reflex.
A: Initial measurement at 175 days old where the rectoanal inhibitory reflex was absent.
B: First follow-up measurement at 272 days old, showing an immature rectoanal inhibitory reflex with limited response in anal sphincter pressure following rectal stimulation.
C: Final follow-up measurement at 733 days old, showing a fully matured rectoanal inhibitory reflex with near-complete relaxation of the anal sphincter.

RAIR could not be elicited. Repeated measurements were performed as no organic cause for the constipation complaints could be identified. A follow-up ARM measurement at 272 days of age subsequently showed an immature RAIR following rectal balloon dilatation. Finally, a measurement at 733 days of age showed a functional, fully matured RAIR, combined with clinical improvement of constipation.

DISCUSSION

As we hypothesized, the cases described in this study illustrate that immaturity of the RAIR can play a role in constipation in a subgroup of infants. Moreover, the symptoms of constipation experienced by these patients and the need for therapeutic aid decreased along with the maturing of the RAIR.

There is a certain ambiguity with regards to an immaturity of the RAIR at birth, with various studies reporting contradictory results.[10–13] For instance, Howard and Nixon concluded that the RAIR is indeed able to mature after birth.[10] They performed anorectal manometry in 60 constipated children of whom three patients initially had no functioning RAIR, but who later developed a functioning RAIR after 22 days of follow-up. In addition to the changes in anorectal physiology, they also noted an improvement of constipation symptoms in these patients. In contrast, there are multiple studies by Benninga and colleagues who demonstrated the RAIR to be functional and matured even in premature infants.[11–13] It must be noted, however, that these studies also contained a few patients in who the authors could not elicit a functioning RAIR. One of these patients subsequently showed a functional RAIR at 12 months follow-up, which supports our finding that in a subgroup of infants, because of unknown reasons, the maturation of the RAIR can be delayed.[12]

At follow-up, despite the continued need for therapeutic aid, there was an overall improvement of symptoms of constipation, based on patients' parents reports and outpatient clinic visits. The residual constipation in these patients could have various causes. First, while we noted an improvement of the RAIR in all patients, it is possible that in some patients the physiology of the anorectum has still not fully matured. Second, as constipation is often the result of a combination of factors, it is possible that factors other than a delayed development of the RAIR continued to cause constipation complaints.[14] For example, these factors could be related to dietary intolerance,[15] low dietary fiber,[16] or psychological stress.[16] And last, at older age, the residual constipation complaints in these patients could have arisen from a behavioral aversion to or learned problems with the process of defecation.[17]

One of the primary limitations of this study was the low number of patients that met the

inclusion criteria, despite the relatively long inclusion period of six years. We offer several reasons for this low number of inclusions. First, as we are a tertiary center, only the most severe cases of infants with constipation are referred to us, thereby limiting the number of patients eligible for inclusion. Given the high incidence of constipation in newborns and infants,[1] we reckon that immaturity of the RAIR may often go unrecognized, as not all children with constipation get referred to a tertiary center,[18] let alone undergo an ARM measurement to test the functioning of the RAIR. Second, the majority of patients in who we could not evoke a RAIR during the initial ARM never underwent a follow-up ARM as their symptoms of constipation had completely diminished. For example, in our recent study on the reliability of ARM in the diagnosis of Hirschsprung's disease we found 27 patients in whom we could not evoke a RAIR, although Hirschsprung's disease had been excluded in these patients.[19] Only a small subgroup of these patients, included in this study, underwent a follow-up measurement. In general, follow-up measurements are unfortunately rarely performed in infants with abnormal anorectal physiology. Proper longitudinal studies are therefore needed to more precisely investigate the development of the RAIR and to determine the effect of this development on constipation symptoms.

A limitation of this study may be the inability to evoke the RAIR during ARM because of insufficient dilatation of the rectal balloon.[19] Failure to sufficiently dilate the rectal balloon may lead to the wrong conclusion that the RAIR is immature or absent. However, given our previous experience with ARM,[19] and the simultaneous decrease of constipation symptoms along with the maturation of the RAIR, it is probable that some form of development has taken place in these patients. Last, each of the included patients in our current study was male, for which we have no clear explanation. Possibly, the differences in genetics or anatomy between males and females may make males more prone to suffer from immaturity of the RAIR. On the other hand, the overrepresentation of males may be the result of mere coincidence.

Conclusion

Immaturity of the RAIR might play a role in severe constipation in a subgroup of newborns and could give a valuable explanation for their complaints. Subsequently, the symptoms of constipation in these patients may improve as the RAIR further matures. During this period sufficient conservative treatment with laxatives and rectal washouts may prevent severe dilatation of the rectum. In patients in whom the RAIR is absent on an initial ARM measurement follow-up ARM measurements should be performed to monitor the development of the anorectal physiology.

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REFERENCES

1 Turco R, Miele E, Russo M, et al. Early-Life Factors Associated With Pediatric Functional Constipation. J Pediatr Gastroenterol Nutr 2014;58:307–312.

2 Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr 2014;58:258–74.

3 Kim J-H. How to interpret conventional anorectal manometry. J Neurogastroenterol Motil 2010;16:437–9.

4 Schnaufer L, Talbert JL, Haller JA, et al. Differential sphincteric studies in the diagnosis of anorectal disorders of childhood. J Pediatr Surg 1967;2:538–543.

5 Lawson JO, Nixon HH. Anal canal pressures in the diagnosis of Hirschsprung's disease. J Pediatr Surg 1967;2:544–552.

6 Scharli AF. Pathophysiology of Classical Hirschsprung's disease. In: Holschneider AM, Puri P, eds. Hirschsprung's Disease and Allied Disorders. Frankfurt, Germany: Springer; 2000:109–125.

7 Rattan SS. The internal anal sphincter: regulation of smooth muscle tone and relaxation. Neurogastroenterol Motil 2005;17 Suppl 1:50–59.

8 Tatekawa Y, Kanehiro H, Kanokogi H, et al. The evaluation of meconium disease by distribution of cathepsin D in intestinal ganglion cells. Pediatr Surg Int 2000;16:53–55.

9 Burki T, Kiho L, Scheimberg I, et al. Neonatal functional intestinal obstruction and the presence of severely immature ganglion cells on rectal biopsy: 6 year experience. Pediatr Surg Int 2011;27:487–490.

10 Howard ER, Nixon HH. Internal anal sphincter. Observations on development and mechanism of inhibitory responses in premature infants and children with Hirschprung's disease. Arch Dis Child 1968;43:569–578.

11 Benninga MA, Omari TI, Haslam RR, et al. Characterization of anorectal pressure and the anorectal inhibitory reflex in healthy preterm and term infants. J Pediatr 2001;139:233–237.

12 Lorijn F de, Omari TI, Kok JH, et al. Maturation of the rectoanal inhibitory reflex in very premature infants. J Pediatr 2003;143:630–633.

13 Lorijn F de, Voskuijl WP, Omari TI, et al. Assessment of the rectoanal inhibitory reflex in preterm infants with delayed meconium passage. J Pediatr Gastroenterol Nutr 2005;40:434–7.

14 Tabbers MM, Boluyt N, Berger MY, et al. Nonpharmacologic treatments for childhood constipation: systematic review. Pediatrics 2011;128:753–61.

15 Iacono G, Cavataio F, Montalto G, et al. Intolerance of Cow's Milk and Chronic Constipation in Children. N Engl J Med 1998;339:1100–1104.

16 Rajindrajith S, Devanarayana NM. Constipation in children: Novel insight into epidemiology, pathophysiology and management. J Neurogastroenterol Motil 2011;17:35–47.

17 Belamarich PF. Constipation. In: Foy JM, Adam HM, eds. Signs and Symptoms in Pediatrics. Elk Grove Village, IL: American Academy of Pediatrics; 2015:119–134.

18 Timmerman MEW, Trzpis M, Broens PMA. The problem of defecation disorders in children is underestimated and easily goes unrecognized: a cross-sectional study. Eur J Pediatr [Epub ahead of print].

19 Meinds RJ, Trzpis M, Broens PMA. Anorectal Manometry May Reduce the Number of

Rectal Suction Biopsy Procedures Needed to Diagnose Hirschsprung Disease. J Pediatr Gastroenterol Nutr 2018;67:322–27.

CHAPTER 5

Solitary rectal ulcer syndrome as a sign of unrecognized Hirschsprung's disease

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SUMMARY

We report on two cases of late diagnosed Hirschsprung's disease. Both cases presented themselves with recurrent solitary rectal ulcer syndrome and were diagnosed with Hirschsprung's disease at 18 and 14 years, respectively. Consequently, we advocate the importance of considering Hirschsprung's disease in pediatric patients with solitary rectal ulcer syndrome.

INTRODUCTION

The diagnosis of Hirschsprung's disease has improved over the past few years and it is diagnosed at increasingly younger ages. Nevertheless, Hirschsprung's disease is still diagnosed after the first year of life in up to 5% of the patients.[1] Patients with a late diagnosis of Hirschsprung's disease variously present with chronic constipation with intermittent episodes of diarrhea, abdominal distension, acute enterocolitis, and/or sigmoid volvulus.[2,3] To our knowledge, literature is limited on solitary rectal ulcers as a presenting symptom of Hirschsprung's disease, as only one Hirschsprung's patient with solitary rectal ulcer syndrome (SRUS) was described before.[4] Consequently, diagnostic tests for Hirschsprung's disease are not included in the standard diagnostic workup of patients with SRUS.[5]

In this case report we describe the medical histories of two pediatric patients with late diagnoses of Hirschsprung's disease and SRUS to illustrate the importance of including anorectal manometry and rectal suction biopsies in the standard diagnostic workup of pediatric patients with SRUS.

CASE REPORTS

Patient 1

In the first patient, who had congenital megacolon, a stoma was created in the transverse colon shortly after birth. As gastrointestinal passage was good and rectal suction biopsies did not confirm Hirschsprung's disease, the stoma was lifted at the age of 6 months. Throughout his childhood, however, the patient suffered from episodes of iron deficiency anemia, rectal bleeding, and constipation. Repeated colonoscopies showed recurrent SRUS (Figure 1A), whereas biopsies taken during the colonoscopies excluded inflammatory bowel disease. Because the complaints recurred, and because the treatment for SRUS (in the form of beclomethason and mesalazine enemas) only helped briefly, resection of the sigmoid was performed at the age of 18 years. Macroscopically, the sigmoid appeared enlarged and dilated. Subsequent microscopic examination of the resected colon showed a non-specific ulceration consistent with SRUS (Figure 1B) and a surprisingly limited number of ganglion cells in the distal resection margin, matching a transitional zone as seen in Hirschsprung's disease. Additionally, along with pronounced anorectal dyssynergia, anorectal manometry revealed that the rectoanal inhibitory reflex was absent, supporting the diagnosis of Hirschsprung's disease.

Patient 2

The second patient suffered from congenital diarrhea and failure to thrive during infancy, upon which parenteral nutrition was initiated. At the time, extensive diagnostic workup (including electron microscopy of duodenal biopsies) failed to reveal the cause of these problems. Eventually, the diarrhea resolved, while growth retardation remained. From the age of 11 years, the patient presented with episodes of iron deficiency anemia, rectal bleeding, and constipation. Three colonoscopies showed persistent SRUS. During hospitalization, severe constipation was suspected as the colon was not properly cleansed after the standard bowel preparations in three subsequent colonoscopies. Upper gastrointestinal contrast series showed an intestinal malrotation without a midgut volvulus while, remarkably, a previous contrast series at the age of 3 months had not shown any evidence of intestinal malrotation. Additionally, at the age of 14 years, a colonoscopy with intensive bowel preparation showed a dilated colon and persistent SRUS.

Due to the similarity between the two patients, we suspected that the second patient might also suffer from undiagnosed Hirschsprung's disease. Indeed, rectal suction biopsies showed aganglionosis and proliferation of acetylcholinesterase positive nerve fibers, confirming the diagnosis of Hirschsprung's disease. Moreover, anorectal manometry revealed an absence of the rectoanal inhibitory reflex, supporting the diagnosis (Figure 2).

A Duhamel procedure at the age of 15 years showed an extremely dilated colon. A fifty centimeters length of colon was resected and the patient received a temporary ileostomy. Furthermore, the intestinal malrotation was corrected. Agenesis of the vermiform appendix was also diagnosed, even though the patient had not previously undergone abdominal surgery.

DISCUSSION

In this case report we describe two pediatric patients who suffered from SRUS, constipation, and chronic anemia, and who were finally diagnosed with Hirschsprung's disease at the age of 18 and 14 years, respectively. In the first patient, the diagnosis was only made after resection of the rectosigmoid which, in retrospect, was inadequate for Hirschsprung's disease. The aim of this case report is, therefore, to draw attention on pediatric patients presenting with SRUS as a possible sign of underlying, misdiagnosed, Hirschsprung's disease. Early detection and proper diagnosis is vital to prevent inadequate treatment strategies.

In pediatric patients, SRUS is an extremely rare and benign disorder. Its clinical

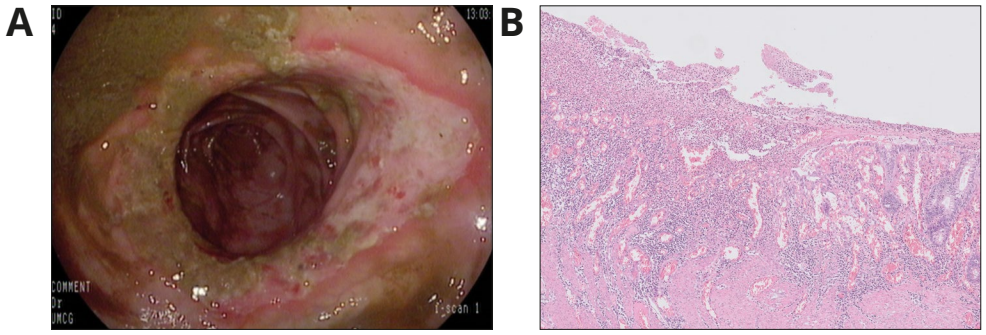

Figure 1
A: Endoscopic findings of a solitary rectal ulcer at the age of 15 years in the first patient.
B: Histological examination of the ulcer after resection of the sigmoid showing findings consistent with SRUS. On the left side non-specific ulceration with granulation tissue and a hyperplastic muscularis mucosae is shown. On the right side preexisting mucosa with erosion, mild inflammation, crypt distortion, and vascular congestion is shown.

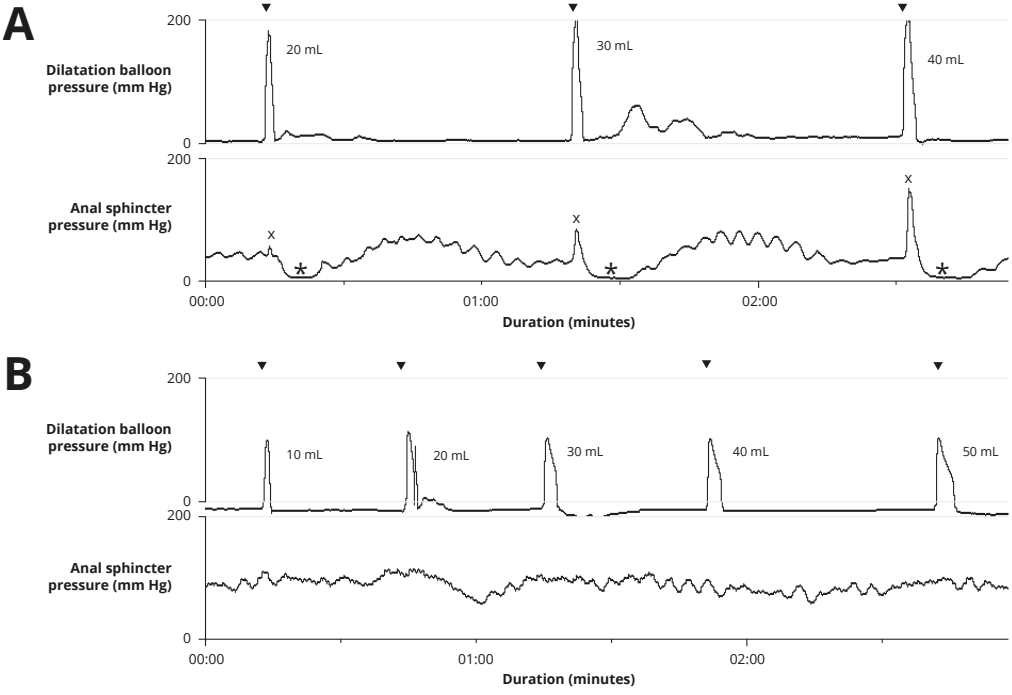

Figure 2
Anorectal manometry measurements showing the presence of the rectoanal inhibitory reflex (denoted by asterisks) in a control subject without Hirschsprung's disease (A), and the absence of the rectoanal inhibitory reflex in the second patient (B). Arrowheads denote the moment of rectal balloon dilation, crosses denote the rectoanal contractile reflex.

presentation is variable, thus complicating the diagnosis.[6,7] Although the etiology of SRUS is incompletely understood, it is thought that local ischemia, and mucosal prolapse as a result of increased rectal pressure, are involved in the pathogenesis of SRUS.[5,8] These factors are also seen in patients with Hirschsprung's disease.[9] While the exact causes of SRUS in the patients described in this report remain unclear, it is possible that an increase of rectal pressure, due to the pathogenesis of Hirschsprung's disease, led to the genesis of SRUS.

To our knowledge, a rectal ulcer in Hirschsprung's disease is mentioned only once in the literature.[4] The presentation of two patients in a relatively short space of time, however, led us to believe that possibly more cases presenting with SRUS are unrecognized cases of Hirschsprung's disease. Further investigations are required to confirm whether at older ages SRUS could indeed be considered as a sign of Hirschsprung's disease.

Previously, it was recommended to examine all pediatric patients with SRUS using defecography and anorectal manometry in order to define an underlying pathophysiological cause.[10] We agree with this suggestion, and in addition, if anorectal manometry cannot exclude Hirschsprung's disease, we strongly advocate performing rectal suction biopsies in any pediatric patient presenting with chronic defecation complaints and blood loss due to SRUS. Adequate treatment for Hirschsprung's disease, even at older ages, might still lead to satisfactory results and improvement of patients' quality of life and could prevent long-term complaints such as growth deprivation and malnutrition.[3]

Basing ourselves on the medical history of these two patients, we conclude that SRUS should be considered as a possible presenting symptom of long-standing, and unrecognized, Hirschsprung's disease. We emphasize the importance of anorectal manometry and rectal suction biopsies as part of the standard diagnostics of pediatric patients with SRUS.

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REFERENCES

1 Suita S, Taguchi T, Ieiri S, et al. Hirschsprung's disease in Japan: analysis of 3852 patients based on a nationwide survey in 30 years. J Pediatr Surg. 2005;40:197–201.

2 Sharma S, Gupta DK. Hirschsprung's disease presenting beyond infancy: surgical options and postoperative outcome. Pediatr Surg Int. 2012;28:5–8.

3 Doodnath R, Puri P. A systematic review and meta-analysis of Hirschsprung's disease presenting after childhood. Pediatr Surg Int. 2010;26:1107–10.

4 Golinsky D, Freud E, Steinberg RM, et al. A stercoraceous ulcer of the colon in neglected Hirschsprung's disease. Pediatr Surg Int. 1998;13:55–7.

5 Zhu QC, Shen RR, Qin HL, et al. Solitary rectal ulcer syndrome: clinical features, pathophysiology, diagnosis and treatment strategies. World J Gastroenterol. 2014;20:738–44.

6 Blackburn C, McDermott M, Bourke B. Clinical presentation of and outcome for solitary rectal ulcer syndrome in children. J Pediatr Gastroenterol Nutr. 2012;54:263–5.

7 de Carpi JM, Vilar P, Varea V. Solitary rectal ulcer syndrome in childhood: a rare, benign, and probably misdiagnosed cause of rectal bleeding. Report of three cases. Dis Colon Rectum. 2007;50:534–9.

8 la Rubia L De, Villaespesa AR, Cebrero M, et al. Solitary rectal ulcer syndrome in a child. J Pediatr. 1993;122:733–6.

9 Chetty R, Govender D. Mucosal prolapse changes in Hirschsprung's disease. Histopathology. 1997;30:324–7.

10 Temiz A, Tander B, Temiz M, et al. A rare cause of chronic rectal bleeding in children; solitary rectal ulcer: case report. Ulus Travma Acil Cerrahi Derg. 2011;17:173–6.

PART II

Defecation disorders in the general population

CHAPTER 6

Reproducibility, feasibility, and validity of the Groningen Defecation and Fecal Continence questionnaires

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SUMMARY

Background

Current questionnaires on defecation disorders are often brief and fail to include questions considering causative factors. Furthermore, adult and pediatric questionnaires differ, which makes it impossible to monitor defecations disorders during the transition from childhood to adulthood. With these points in mind we developed the Groningen Defecation and Fecal Continence (DeFeC) questionnaire and its pediatric equivalent, the P-DeFeC. The aim of this paper is to introduce the questionnaires and to assess their feasibility, reproducibility, and validity.

Methods

Various Rome IV criteria and scoring tools for constipation and fecal incontinence were incorporated, resulting in nine categories. Feasibility and reproducibility were assessed by performing a test-retest survey in 100 adult participants. Concurrent validity was assessed in 27 patients and 18 healthy volunteers by comparing questionnaire-based diagnoses of constipation and fecal incontinence to final diagnoses based on anorectal function tests.

Results

There were no remarks on the understandability of any questions. The Cohen's kappa coefficient of all main questions ranged from 0.26 to 1.00, with an average of 0.57. All but one category showed moderate agreement or higher. The sensitivity of the questionnaire-based diagnosis of constipation was 75%; specificity was 100%. The sensitivity of the questionnaire-based diagnosis of fecal incontinence was 77%; specificity was 94%.

Conclusions

Overall reproducibility of the Groningen DeFeC questionnaire is acceptable and its validity is good. This makes it a feasible screening tool for defecation disorders and, equally important, with these questionnaires defecation disorders can now be monitored during the transition from childhood to adulthood.

INTRODUCTION

Fecal disorders, such as constipation and fecal incontinence, are among the most common medical disorders. In the general population the prevalence of constipation is 16%[1] and for fecal incontinence it is 8%.[2] Despite their high rates of prevalence, constipation and fecal incontinence are not yet clearly defined, because the symptoms vary widely among patients and are often ambiguous. This explains why diagnosing constipation and fecal incontinence, and finding the causative factors, remains difficult.

Ambiguity regarding the definitions of defecation disorders led to the development of the Rome criteria[3,4] and different questionnaires, each with their own scoring systems.[5–19] To our knowledge, even though constipation and fecal incontinence are known to coexist, only one of these scoring systems incorporates both disorders.[5] Moreover, only a few questionnaires include questions relating to factors that may influence defecation disorders, such as diet and therapy,[7–12] and only one questionnaire includes questions relating to other causative factors for constipation and fecal incontinence, such as obstetric history, medicine use, or neurological illnesses.[6] Finally, and most importantly, all the questionnaires that are currently available are designed separately for children or adults. This makes it impossible to determine whether symptoms of constipation and fecal incontinence in pediatric patients change during the transition from childhood to adulthood, even though continuity of care during this transitional phase is an important issue.

Keeping all these points in mind we developed the Groningen Defecation and Fecal Continence (DeFeC) questionnaire, a comprehensive questionnaire that contains questions on anorectal functioning, associated disorders, and causative factors and its pediatric equivalent, the Pediatric DeFeC questionnaire (P-DeFeC). We based the questionnaires on the adult Rome IV criteria[3,4] for constipation and fecal incontinence, along with several validated constipation and fecal continence scores.[10–14] The aim of this paper is to introduce the two versions of the questionnaire and to explain their contents. In addition, we aimed to assess the reproducibility, feasibility, and validity of the adult version of the DeFeC questionnaire.

METHODS

Design of the Groningen DeFeC questionnaire

The Groningen DeFeC questionnaire was modeled on the Rome IV questionnaire,[20] the Rome IV criteria,[3,4] and various validated scoring tools.[10–14] We recruited patients, fellow physicians, and acquaintances to review the draft questionnaire and we obtained their

remarks on the understandability of the questions and of the language used in the questionnaire. The final version of the questionnaire consisted of 88 questions in nine different categories that covered various aspects of anorectal functioning, associated disorders, and causative factors (Table 1, and see the appendices for the complete version of the questionnaire). All the questions relate to a patient's bowel habits during the last six months. Below, we briefly explain the contents of the categories of the questionnaire:

0. Prior to the questions on bowel habits, we included several questions on demography. These questions were included primarily to collect reference data from the general population. They also allow future matching and comparisons between the patient data to the data of healthy peers. These questions do not have to be completed for the calculation of the various Rome IV criteria and scoring tools.
1. Defecation pattern was assessed by frequency and stool consistency. The options for defecation frequency ranged from less than once a month to more than five times a day. Stool consistency was defined in accordance with the stool types as described in the Bristol stool form scale.[21]
2. Constipation-related aspects were investigated more thoroughly than is done in current questionnaires. Patients were first asked whether they have difficulty emptying their bowels and, if so, how long had they suffered from these symptoms. The following questions allowed us to determine whether the patients fulfilled the Rome IV criteria for functional constipation. Dyssynergic defecation was assessed by inquiring about the most characteristic symptoms: excessive straining, duration of strain, anal blockage, incomplete defecation, failure to defecate, and anal pain. Because symptoms of constipation are often associated with abdominal bloating and pain, we added questions specifying abdominal discomfort.
3. A patient's daily diet is known to play a role in constipation.[22] Inquiring about diet can be troublesome and should preferably be addressed by using a dietary diary. Processing such a diary, however, is time-consuming – both for the patient and the physician. Instead, we decided to screen patients' dietary habits by asking four questions about intake of liquids and consumption of fruits, vegetables, and whole-wheat bread. Using various remedies to relieve constipation is common practice among patients with constipation problems. We therefore added detailed questions on the use of laxatives, as well as questions relating to other constipation remedies, such as rectal suppositories and rectal irrigation. Lastly, we added a question on help-seeking behavior for constipation symptoms.
4. Fecal incontinence was assessed by multiple questions relating to different types of incontinence, such as soiling, incontinence for solid stool, liquid stool, and

flatus. A positive answer to one of the aforementioned questions was followed by more detailed questions relating to severity and frequency of fecal incontinence. Other questions regarding incontinence related to the use of stool-hardeners, pads, rectal irrigation, and changes in daily activities. Finally, we asked patients about help-seeking behavior regarding their incontinence symptoms.

5. Both the ability to feel the urge to defecate and the ability to postpone the passage of stools play an important role in fecal continence. We asked patients whether they feel the urge to defecate before going to the toilet and whether they can differentiate between different kinds of stools and flatus. We also asked how long

Table 1
Contents of the Groningen DeFeC questionnaire

Categories	Questions	No. of questions
Demographic information	General information such as height, weight, gender, age, residence, and daily occupation	8
Defecation pattern	Defecation frequency, stool consistency	2
Constipation complaints	Difficulties passing stool, incomplete or failure to defecate, anal pain, bloating, and abdominal discomfort/pain	16
Constipation-related remedies	Use of diet, laxatives, and/or more invasive therapies	14
Fecal continence	Different types of incontinence (*i.e.* soiling, solid, liquid, gas), time of incontinence, and incontinence related therapies	16
Anorectal sensation and voluntary contractions	Urge to defecate, ability to hold stool, ability to differentiate between various stool types.	4
Urinary continence	Urination frequency, straining during urination, urinary incontinence, time of incontinence, nocturnal urination, and urinary tract infections.	9
Obstetric and gynecologic history	Obstetric history and complications, gynecologic surgical history, and prolapse complaints	11
Pelvic floor-related medical history	Bowel surgery history, presence of blood or slime in stools, medical conditions affecting bowel movements, and overall medication use	8
	Total:	88

they are able to postpone the passage of stools and how often they have to hurry to reach the toilet in time.

6. Fecal and urinary incontinence frequently coexist, especially in the elderly and nursing home residents.[23] For this reason we also included several questions on urinary continence and urinary tract infections.
7. For female respondents we included a category on obstetric and gynecologic medical history. We included detailed questions on the number of deliveries, types of delivery, and complications during delivery.
8. The last category of the Groningen DeFeC questionnaire inquired about the patient's medical history regarding bowel surgery, somatic bowel diseases, and other diseases that could influence anorectal physiology.

Pediatric version of DeFeC questionnaire

The P-DeFeC questionnaire is the pediatric equivalent of the Groningen DeFeC questionnaire (see the supplementary files for the complete version). It contains almost the same questions and criteria as the adult version, but is more simply worded, thus making it understandable for a child of eight years or older. Questions on educational level, work, and obstetric history were removed as such questions would be irrelevant to most children. The pediatric version therefore consisted of 79 questions in eight different categories instead of the 88 questions in the adult version.

Completing the questionnaires

Both versions of the questionnaire are self-administered and can be completed either online or on paper. The questionnaires were designed in such a way that patients would not be asked questions that were irrelevant to them. This is determined by positive or negative answers given at the beginning of certain categories. For instance, if patients reported never to experience abdominal pain, they could skip the subsequent questions on abdominal pain. In this way an adult male respondent who does not suffer from either constipation or fecal incontinence only needed to answer 55 out of the total set of 88 questions.

Assessing defecation disorders

The Groningen DeFeC questionnaire includes questions that comply with several adult Rome IV criteria, as well as validated constipation and fecal incontinence scores. Firstly, we defined constipation in accordance with the Rome IV criteria for functional constipation[3] and we assessed its severity with the Constipation Scoring System as described by Agachan and colleagues.[10] In addition, we included a disease-specific

score for obstructed defecation syndrome by Renzi and colleagues.[12] We defined fecal incontinence in accordance with the Rome IV criterion for fecal incontinence, which is recurrent uncontrolled passage of fecal material.[4] We assessed the severity of fecal incontinence in terms of the Continence Grading Scale as described by Jorge and Wexner[13] and the Vaizey incontinence score.[11] Lastly, fecal incontinence following lower anterior resection surgery can be assessed with the lower anterior resection score developed by Emmertsen and Laurberg.[14]

The P-DeFeC questionnaire consisted of the same criteria and scores for constipation and fecal incontinence as the adult version. This enabled us to compare defecation disorders during the transition from childhood to adulthood. Additionally, in contrast to the adult Rome IV criteria for constipation, the pediatric Rome IV criteria required a psychical examination.[24] Because this questionnaire was designed as a screening tool, physical examination is not possible. For these reasons we decided to incorporate the same adult Rome IV criteria for constipation and fecal incontinence in the P-DeFeC questionnaire as in its adult equivalent.

Questionnaire translation

Both versions of the DeFeC questionnaire were translated from Dutch to English and back to Dutch to ascertain that the contents of the questionnaires had not changed in the translation process. First, a bilingual translator, whose mother tongue was English and who had no knowledge of the subject, translated the questionnaire from Dutch to English. Subsequently, the questionnaires were translated back to Dutch by another bilingual translator whose mother tongue was Dutch and who also had no knowledge of the subject. The agreement of the contents between the Dutch original and the English-back-to-Dutch translation were analyzed. Any discrepancies were documented, discussed, resolved, and adjusted accordingly in the English version of the questionnaire. In this way we established that to all intents and purposes the contents of the English translation of both versions of the DeFeC questionnaire were the same as the Dutch original. A few items, such as the question on educational level and the four questions on dietary habits, were tailored to Dutch standards. A minimal cross-cultural adaptation is therefore required before the questionnaires can be used in other countries.

Reproducibility

To test the reproducibility, that is the replicability of the instrument, we performed a test-retest survey by asking 100 adult participants to complete the Groningen DeFeC questionnaire twice, with a one-month interval in between. The participants were recruited from the general Dutch population by an external company specialized in

conducting surveys (Survey Sampling International, Rotterdam, the Netherlands). The test-retest survey was only performed in adults as we found it unethical to subject children to this survey twice.

Feasibility

The initial draft was modified on the basis of the remarks made by the patients, physicians, and acquaintances in such a way that the questions and answers were understandable to someone with a basic level of education. At the end of the survey, in order to test feasibility, the adult participants of the test-retest survey were given the opportunity to remark on the contents of the questionnaire and their ability to complete the questionnaire. We also assessed the time required to fully complete the P-DeFeC and DeFeC questionnaires using data obtained from previously performed studies in the general population.[25,26]

Validity

In order to test validity, that is the degree to which the questionnaire truly measures the construct it claims to measure,[27] we analyzed the sensitivity and specificity of questionnaire-based diagnoses using anorectal function tests as the gold standard. The anorectal functions tests were only performed in adults as we found it unethical to subject children to these tests for the purpose of validating our questionnaire.

The questionnaire-based diagnosis of constipation was based on the Rome IV criteria for functional constipation,[3] whereas the balloon evacuation test was used as the gold standard for constipation. After the balloon evacuation test, constipation was defined as the inability to pass a rectal balloon filled with a minimum of 50 mL within two minutes.[28] The questionnaire-based diagnosis of fecal incontinence was based on the Rome IV criteria for fecal incontinence,[4] whereas the rectal infusion test was used as the gold standard. After the rectal infusion test, fecal incontinence was defined by involuntary leakage of liquid following the infusion of 1000 mL of water at body temperature.[29,30]

We measured the ability to correctly identify positives by assessing the sensitivity in patients who were unable to expel the rectal balloon (that is who suffered from constipation) or who experienced leakage during the rectal infusion test (that is who suffered from fecal incontinence). We measured the ability to correctly identify negatives by assessing the specificity in healthy adult volunteers who expelled the rectal balloon effortlessly (that is who did not suffer from constipation) or who experienced no leakage (that is who did not suffer from fecal incontinence).

Statistics

The data were analyzed using SPSS 23.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY). After the test-retest survey we analyzed the reproducibility of the questions of the questionnaire by calculating the weighted Cohen's kappa (κ) coefficient for questions with multiple categorical response options and the unweighted κ coefficient for questions with a 'yes' or 'no' response option. We analyzed the reproducibility of criteria for functional constipation and fecal incontinence, based on the Rome IV diagnostic criteria, by using the unweighted κ coefficient. The reproducibility of continuous defecation scores, such as the Constipation Scoring System and the Continence Grading Scale, was analyzed by using the intraclass correlation coefficient (ICC).

The calculated κ coefficients and ICC values ranged between -1 and 1, where a negative value indicates poorer than chance agreement. Positive values below 0.2 indicate slight agreement, values between 0.21 to 0.40 indicate fair agreement, values between 0.41 to 0.60 indicate moderate agreement, values between 0.61 to 0.8 indicate substantial agreement, and values between 0.81 to 1.0 indicate almost perfect agreement.[31]

RESULTS

Reproducibility

One hundred adult individuals participated in the test-retest survey, consisting of 50% (n = 50) female respondents and 50% (n = 50) male respondents. Respondents' median age was 43 years, with a minimum of 19 years and a maximum of 65 years. Based on the

Table 2
Reproducibility of the adult version of Groningen DeFeC questionnaire

Category	κ coefficient*	Interpretation**
Defecation pattern	0.48	Moderate
Constipation complaints	0.54	Moderate
Constipation-related remedies	0.73	Substantial
Fecal continence	0.39	Fair
Anorectal sensation and voluntary contractions	0.44	Moderate
Urinary continence	0.60	Moderate
Obstetric and gynecologic history	0.81	Almost perfect
Pelvic floor-related medical history	0.50	Moderate
Average:	0.57	Moderate

* Weighted Cohen's kappa (κ) coefficient

** Interpretation of κ coefficients according to Landis and Koch[31]

primary survey, 20% (n = 20) of the respondents were eligible for the Rome IV criteria of functional constipation, while 7% (n = 7) were eligible for the Rome IV criteria of fecal incontinence.

When analyzing reproducibility of all the main questions of the adult version of the Groningen DeFeC questionnaire we found that the weighted κ coefficient ranged from 0.26 to 1.00, with an average of 0.57, indicating a moderate agreement for the entire questionnaire (Table 2). Additionally, the average weighted κ coefficients for each separate category of the Groningen DeFeC questionnaire were calculated and ranged from 0.39 to 0.81 (Table 2). All but one category showed moderate agreement or higher.

We also analyzed the reproducibility of scoring the Rome IV criteria for functional constipation and fecal incontinence (Table 3). The unweighted κ coefficient for functional constipation was 0.41 (95% CI, 0.18 to 0.64), indicating moderate agreement. The coefficient for fecal incontinence was 0.26 (95% CI, -0.08 to 0.60), indicating fair agreement. Finally, we analyzed the reproducibility of two validated scores for severity of constipation and fecal incontinence, that is for the scores obtained with the Constipation Scoring System and Continence Grading Scale. Both scores showed substantial agreement, 0.73 (95% CI, 0.63 to 0.81) for the Constipation Scoring System and 0.64 (95% CI, 0.51 to 0.74) for the Continence Grading Scale (Table 3).

Feasibility

All 100 adult participants in our test-retest survey fully completed the questionnaire twice. There were no remarks on the understandability of any of the items. On average it took less than 11 minutes to complete the DeFeC and 8 minutes for P-DeFeC.

Table 3
Reproducibility of criteria and scores

	Reproducibility		
Rome IV criteria	κ coefficient*	95% CI	Interpretation**
Functional constipation	0.41	(0.18 to 0.64)	Moderate
Fecal incontinence	0.26	(-0.08 to 0.60)	Fair
Scores	ICC	95% CI	Interpretation**
Constipation Scoring System[10]	0.73	(0.63 to 0.81)	Substantial
Continence Grading Scale[13]	0.64	(0.51 to 0.74)	Substantial

* Unweighted Cohen's kappa (κ) coefficient

** Interpretation of κ coefficients according to Landis and Koch[31]

Validity

For the assessment of validity we included 27 referred adult patients, 74% (n = 20) of whom were women and 26% (n = 7) were men. The patients' median age was 55 years and ranged from 18 years to 75 years. We only included patients who suffered from constipation (n = 8), and/or from fecal incontinence (n = 22), based on anorectal function testing. Additionally, we included 18 healthy volunteers, 56% (n = 10) of whom were women and 44% (n = 8) were men. The healthy volunteers' median age was 22 years and ranged from 19 years to 26 years. We only selected healthy volunteers who did not suffer from constipation and fecal incontinence based on anorectal function testing.

The sensitivity of the questionnaire-based diagnosis of constipation was 75% and specificity was 100% (Table 4). Likewise, the sensitivity of the questionnaire-based diagnosis of fecal incontinence was 77% and specificity was 94% (Table 4).

DISCUSSION

We developed the Groningen DeFeC questionnaires using existing criteria and validated scoring tools. It contained questions about anorectal functioning and associated disorders, such as constipation, fecal incontinence, and their combined forms. Because of their extensive range, which included urologic and gynecologic questions, the Groningen DeFeC questionnaires are a feasible tool to not only screen for defecation disorders, but to also determine causative factors. The questionnaires can be used to assess the adult Rome IV criteria for fecal incontinence and constipation,[3,4] as well as several fecal incontinence and constipation scores.[10–14] This makes the Groningen DeFeC questionnaire an excellent tool of choice in day-to-day clinical practice and for scientific studies. Importantly, this questionnaire has a pediatric version that consists of the same questions and scores. This provides the possibility to compare defecation disorders before and after the transition from childhood to adulthood.

To assess whether this questionnaire is understandable and easy to complete, whether it is reliable, and whether it measures what it claims to measure we analyzed

Table 4

Diagnostic accuracy of questionnaire-based diagnoses

	Sensitivity		Specificity	
Rome IV criteria	No.	%	No.	%
Functional constipation	6/8	75	18/18	100
Fecal incontinence	17/22	77	17/18	94

its feasibility, reproducibility, and validity in adult participants. For ethical reasons we did not perform the validation process in children. Nevertheless, we expect the outcomes to be comparable, because the questions are almost the same albeit that they were worded more simply than in the adult version of the Groningen DeFeC questionnaire.

Regarding feasibility, the questionnaire proved easy to understand and easy to complete. This was illustrated by our trial runs, such as this study and other studies in samples of the Dutch general population[25,26] that yielded only a small number of remarks from the participants, none of which concerned the understandability of the questionnaire. Although the questionnaire consisted of a wide range of questions, on average it only required 11 minutes to complete the adult version of the questionnaire and 8 minutes to complete the pediatric version. This also indicates that the questions were easy to understand and easy to answer. The relatively short time required to complete the questionnaires was partially the result of allowing patients to skip questions that are irrelevant to them, based on positive or negative answers given at the beginning of certain categories.

A test of reproducibility showed that the agreement between the two surveys was moderate, with all but one category in the questionnaire showing moderate agreement or higher. We point out that the κ coefficients are reduced due to the low frequency of positive responses in certain categories.[32] This was the case in the category on fecal incontinence especially, which only applied to seven of the 100 respondents. This low number of positive responses may have resulted in a lower κ value and agreement for this specific category. This was also reflected by a mere fair agreement of the Rome IV criteria of fecal incontinence. Moreover, the Rome IV criteria for functional constipation showed moderate agreement, while the scores for both severity of constipation and fecal incontinence showed substantial agreement.

The validity of the questionnaire was good as indicated by a relatively high specificity and sensitivity. This means that the questionnaire can be used to either exclude or confirm whether a patient is suffering from constipation or fecal incontinence-related symptoms. Due to the absence of a gold standard for constipation and fecal incontinence, we chose to use the balloon expulsion and rectal infusion tests for constipation and fecal incontinence, respectively, because these tests are performed routinely in our Anorectal Physiology Laboratory. These tests are also used by other medical centers to investigate these defecation problems.[28–30] Nevertheless, it remains difficult to establish a gold standard for constipation and fecal incontinence, because both disorders consist of a range of symptoms, often reported by the patient, and thus difficult to objectify by means of a test or by the physician. We are confident, however, that the balloon expulsion test can discriminate between severely constipated and healthy individuals, while the rectal

infusion test will easily discriminate between individuals with severely impaired fecal continence and those with perfect fecal continence.

Conclusions

The Groningen DeFeC questionnaires are comprehensive questionnaires that contain questions on anorectal functioning, associated disorders, and causative factors. Importantly, these questionnaires provide the possibility to monitor symptoms and treatment efficacy of defecation disorders during the transition from childhood to adulthood. The adult version of the Groningen DeFeC questionnaire is well understood by the respondents, its reproducibility is acceptable, and its validity is good. Some cross-cultural adaptations will be necessary to extend the use of the questionnaire to other countries, and further use of the questionnaire is necessary to extend its validation in patient populations. Recently, we administered the questionnaire to a sample of the general Dutch population with the purpose of establishing norms to be used in future clinical studies.26 We therefore encourage fellow researchers to also use the Groningen DeFeC questionnaire, or its pediatric equivalent, in clinical studies on fecal disorders.

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REFERENCES

1 Mugie SM, Benninga MA, Lorenzo C Di. Epidemiology of constipation in children and adults: A systematic review. Best Pract Res Clin Gastroenterol. 2011;25:3–18.

2 Whitehead WE, Borrud L, Goode PS, et al. Fecal Incontinence in US Adults: Epidemiology and Risk Factors. Gastroenterology. 2009;137:512–517.e2.

3 Lacy BE, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology. 2016;150:1393–1407e5.

4 Rao SSC, Bharucha AE, Chiarioni G, et al. Functional Anorectal disorders. Gastroenterology. 2016;150:1430–1442e4.

5 Osterberg A, Graf W, Karlbom U, et al. Evaluation of a questionnaire in the assessment of patients with faecal incontinence and constipation. Scand J Gastroenterol. 1996;31:575–80.

6 Reilly WT, Talley NJ, Pemberton JH, et al. Validation of a questionnaire to assess fecal incontinence and associated risk factors: Fecal Incontinence Questionnaire. Dis Colon Rectum. 2000;43:146-53-4.

7 Knowles CH, Eccersley AJ, Scott SM, et al. Linear discriminant analysis of symptoms in patients with chronic constipation: validation of a new scoring system (KESS). Dis Colon Rectum. 2000;43:1419–26.

8 Garrigues V, Galvez C, Ortiz V, et al. Prevalence of constipation: agreement among several criteria and evaluation of the diagnostic accuracy of qualifying symptoms and self-reported definition in a population-based survey in Spain. Am J Epidemiol. 2004;159:520–6.

9 Chan AO, Lam KF, Hui WM, et al. Validated questionnaire on diagnosis and symptom severity for functional constipation in the Chinese population. Aliment Pharmacol Ther. 2005;22:483–8.

10 Agachan F, Chen T, Pfeifer J, et al. A constipation scoring system to simplify evaluation and management of constipated patients. Dis Colon Rectum. 1996;39:681–5.

11 Vaizey CJ, Carapeti E, Cahill JA, et al. Prospective comparison of faecal incontinence grading systems. Gut. 1999;44:77–80.

12 Renzi A, Brillantino A, Sarno G Di, et al. Five-item score for obstructed defecation syndrome: study of validation. Surg Innov. 2013;20:119–25.

13 Jorge JM, Wexner SD. Etiology and management of fecal incontinence. Dis Colon Rectum. 1993;36:77–97.

14 Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. Ann Surg. 2012;255:922–8.

15 Frank L, Kleinman L, Farup C, et al. Psychometric validation of a constipation symptom assessment questionnaire. Scand J Gastroenterol. 1999;34:870–7.

16 Adelstein B-A, Irwig L, Macaskill P, et al. A self administered reliable questionnaire to assess lower bowel symptoms. BMC Gastroenterol. 2008;8:8.

17 Varma MG, Wang JY, Berian JR, et al. The constipation severity instrument: a validated measure. Dis Colon Rectum. 2008;51:162–72.

18 Digesu GA, Panayi D, Kundi N, et al. Validity of the Rome III Criteria in assessing constipation in women. Int Urogynecol J. 2010;21:1185–93.

19 de la Portilla F, Calero-Lillo A, Jimenez-Rodriguez RM, et al. Validation of a new scoring system: Rapid assessment faecal incontinence score. World J Gastrointest Surg. 2015;7:203–7.

20 Palsson OS, Whitehead WE, Van Tilburg MAL, et al. Development and validation of the Rome

IV diagnostic questionnaire for adults. Gastroenterology. 2016;150:1481–91.
21 Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32:920–4.
22 Muller-Lissner SA, Kamm MA, Scarpignato C, et al. Myths and misconceptions about chronic constipation. Am J Gastroenterol. 2005;100:232–42.
23 Chiang L, Ouslander J, Schnelle J, et al. Dually incontinent nursing home residents: clinical characteristics and treatment differences. J Am Geriatr Soc. 2000;48:673–6.
24 Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: Child/adolescent. Gastroenterology. 2016;150:1456–1468e2.
25 Timmerman MEW, Trzpis M, Broens PMA. The problem of defecation disorders in children is underestimated and easily goes unrecognized: a cross-sectional study. Eur J Pediatr [Epub ahead of print].
26 Meinds RJ, Van Meegdenburg MM, Trzpis M, et al. On the prevalence of constipation and fecal incontinence, and their co-occurence, in the Netherlands. Int J Colorectal Dis. 2017;32:475–83.
27 Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol. 2010;63:737–45.
28 Chiarioni G, Kim SM, Vantini I, et al. Validation of the Balloon Evacuation Test: Reproducibility and Agreement With Findings From Anorectal Manometry and Electromyography. Clin Gastroenterol Hepatol. 2014;12:2049–54.
29 Read NW, Haynes WG, Bartolo DC, et al. Use of anorectal manometry during rectal infusion of saline to investigate sphincter function in incontinent patients. Gastroenterology. 1983;85:105–13.
30 Rao SS. Manometric evaluation of defecation disorders: Part II. Fecal incontinence. Gastroenterologist. 1997;5:99–111.
31 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159–74.
32 Cicchetti D V, Feinstein AR. High agreement but low kappa: II. Resolving the paradoxes. J Clin Epidemiol. 1990;43:551–8.

CHAPTER 7

On the prevalence of constipation and fecal incontinence, and their co-occurrence, in the Netherlands

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SUMMARY

Background

Numerous studies have investigated the prevalence of constipation and fecal incontinence (FI) in the general population and, even though these disorders are known to co-occur, they were studied independently of each other. Our aim was to investigate the prevalence of constipation and FI, and their co-occurrence, in the general population in the Netherlands.

Methods

We studied a cross-section of the Dutch population (N = 1259). All respondents completed the Groningen Defecation & Fecal Continence questionnaire. We defined constipation and FI in accordance with the Rome III criteria.

Results

We found that 24.5% (95% CI, 22.1–26.8) suffered from constipation, 7.9% (95% CI, 6.4–9.4) suffered from FI, and 3.5% (95% CI, 2.5–4.5) suffered from both disorders. Constipated respondents were 2.7 times more likely to suffer from FI than non-constipated respondents (95% CI, 1.8–4.0). Moreover, 48.7% of the respondents with constipation, 35.0% with FI, and 38.6% in whom the disorders co-occurred qualified their bowel habits as either "good" or "very good". We found that 49.4% of the respondents with constipation and 48.0% with FI had not discussed their complaints with anyone.

Conclusions

Constipation and FI, isolated or co-occurring, are common disorders in the general population, even in young and healthy respondents. Since constipation and FI often co-occur, we recommend that patients who seek medical attention for either disorder should be examined for both. Moreover, constipation and/or FI are not always identified appropriately by patients. Therefore physicians should take the initiative to diagnose and treat these disorders.

INTRODUCTION

Bowel habits and associated disorders, such as constipation and fecal incontinence (FI) are very private and are therefore rarely discussed by patients. Even in the consulting room these matters are seldom addressed if they are not the primary reason for visiting a doctor. This could be due to embarrassment on the part of the patient or due to lack of knowledge and/or interest on the part of the physician.[1] Alternatively, patients could simply be unaware of the fact that their defecation habits might not be considered normal.

Due both to ignorance and the stigma attached to this subject, the impact of constipation and FI on the general population has long been unclear. Over the last decades, however, numerous studies were performed investigating the bowel habits in the general population in various countries including Taiwan, the United States of America, Iran, Greece, Italy, and Australia. These studies found that constipation and FI have a prevalence of 2.5% to 22.8%[2–9] and 7.2% to 12.1%,[8–11] respectively. Albeit, these studies considered constipation and FI independently of each other and neglected to investigate the co-occurrence of the two disorders. While the effect of constipation on FI is well-known in children and geriatric patients,[12] to date the frequency of the co-occurrence of constipation and FI has not been investigated in the general population. Nor has a population-based study on bowel habits ever been performed in the Netherlands, even though such a study is vital for assessing the impact and burden of these disorders on Dutch society.

Our primary aim, therefore, was to investigate the prevalence of constipation and FI in the Dutch population, as well as the co-occurrence of the two disorders. We hypothesize that, given the high prevalence of both disorders, a significant group of the population will suffer from both disorders. Our second aim was to investigate how respondents qualified their own health regarding the ability to hold and pass stools, and how often they sought medical help for their defecation complaints.

METHODS

Study design

We examined a cross-section of the Dutch population between September 1 and November 1, 2015. In order to obtain representative data we commissioned Survey Sampling International (Rotterdam, the Netherlands), a company specialized in performing surveys, to draw a population-based sample from a database of respondents. The participants in this database were sent a link that enabled them to fill out the Groningen Defecation &

Fecal Continence (DeFeC) questionnaire on their computer (see appendices). The lower age limit for inclusion we set at 18 years, while there was no upper age limit. Out of a total of 3031 eligible respondents who started filling out the questionnaire, 1642 (54.2%) filled it out completely. Subsequently, a random selection of these questionnaires was made by Survey Sampling International to arrive at a representative cohort, equally distributed regarding gender, region, and age according to the population pyramid of the Netherlands as reported by Statistics Netherlands.[13] By doing so, 1259 out of 1642 (76.7%) questionnaires were included in our analysis.

Assessment of constipation and fecal incontinence

We defined constipation according to the Rome III criteria for constipation.[14] These criteria consist of the following items: straining, lumpy or hard stools, incomplete evacuation, anorectal blockage, manual maneuvers to facilitate defecation, and reduced stool frequency. In order to meet the criteria for constipation the respondents had to have at least two of the aforementioned complaints, plus rarely having loose stools without the use of laxatives. We also defined FI according to the Rome III criteria for FI, *i.e.* recurrent uncontrolled passage of fecal material (including soiling) at least several times per month, for the last three months.[15] We performed a subanalysis to determine from which type of FI the respondents suffered. Soiling was defined as the loss of small amounts of feces or staining of underwear, urge FI as being unable to reach the toilet in time after feeling a urge sensation, liquid stool FI as loss of watery stools or diarrhea, and solid stool FI as loss of large amounts of solid feces without having felt urge.

Assessment of bowel-related quality of life and help-seeking behavior

We also asked respondents how they would qualify their ability to hold and pass stools. Furthermore, if they suffered from constipation, FI or both, we asked whether the respondents ever talked about their defecation problems to someone (for example family, friends, general practitioner, medical specialist, or other).

Data analysis

In order to analyze the prevalence of constipation and FI at different ages, we divided the respondents into five groups on the basis of their age percentiles: 18 to 34, 35 to 46, 47 to 55, 56 to 64, and 65 to 85-year-olds. We first analyzed the entire group of respondents, irrespective of whether they suffered from any comorbidity known to influence defecation pattern and fecal continence. By so doing, we defined the true rate of constipation and FI of the total Dutch population. Subsequently, we performed a subanalysis to define the rate of constipation and FI in the “healthy” Dutch population,

i.e. that part of the population which did not experience any disease that could negatively influence bowel habits and continence. Thus, we excluded respondents who had a history of bowel surgery (for example intestinal resection, perianal fistula operation, anal sphincter operation, hemorrhoid operation, prostate operation) or respondents who suffered from somatic diseases that could influence their bowels, such as rectal prolapse, inflammatory bowel diseases, diabetes, cerebral stroke, neurological disorders (for example spinal cord injury, multiple sclerosis), slow transit constipation, or congenital disorders (for example anorectal malformation, Hirschsprung's disease, sacrococcygeal teratoma, or spina bifida).

Statistical analysis

Data were analyzed with SPSS 23.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Proportions were reported as prevalence percentages, and were reported with the corresponding 95% confidence intervals (CIs). Comparison between proportions was made using Pearson's chi-square test. Proportions were additionally used to

Table 1
Respondent characteristics

	No.	%
Overall	1259	100.0
Gender		
Male	579	46.0
Female	680	54.0
Age (years)		
18-34	273	21.7
35-46	256	20.3
47-55	253	20.1
56-64	234	18.6
65-85	243	19.3
Highest educational level		
Primary	260	20.7
Secondary	505	40.1
Tertiary	494	39.2
Employed		
Yes	624	49.6
No	635	50.4
Residence		
Rural	436	34.6
Urban	823	65.4
Co-morbidities influencing bowel pattern		
Yes	251	19.9
No	1008	80.1

calculate odds ratios (ORs) between groups, reported with the corresponding 95% CIs. The probabilities of constipation and/or FI were defined by the number of respondents with constipation and/or FI, respectively, divided by the total number of respondents at any age. The relationship between age and the probability of constipation and FI was evaluated by spline regression analysis using Stata 14 (StataCorp, College Station, TX). Two-sided *P* values of less than .050 were considered statistically significant. Figures were generated using GraphPad Prism 5.04 (GraphPad Software Inc., La Jolla, CA).

RESULTS

Respondent characteristics

A total of 1259 questionnaires were completed entirely by 46.0% (n = 579) male respondents and 54.0% (n = 680) female respondents, with a median age of 49 years (Table 1). At the time of filling out the questionnaire, 50.4% (n = 635) of the respondents were either unemployed or did not hold a job for various reasons, such as household commitments/raising children (5.9%), pre-pension/pension (20.3%), study (4.0%), health-related problems (9.9%), or involuntary unemployment (10.5%). A total of 19.9% (n = 251) of the respondents reported suffering from somatic diseases that could potentially influence their bowel patterns and fecal continence or reported having a history of bowel surgery.

Prevalence and probability of constipation

Firstly, we analyzed the prevalence of constipation for gender and different age groups (Table 2). Overall, 24.5% (95% CI, 22.1–26.8) of the respondents suffered from constipation. Females were 1.8 times more likely to suffer from constipation than males (95% CI, 1.4–2.3). Moreover, the prevalence of constipation decreased with increasing age (Table 2, $P < .001$). Because we found a significant difference in the prevalence of constipation between different age groups, we analyzed how the probability of constipation changed with age (Figure 1A). The probability of constipation gradually decreased to a minimum of approximately 0.17 at 61 years. After this initial decrease we found an increase in the probability of constipation as respondents' ages increased beyond 61 years of age.

Prevalence and probability of fecal incontinence

Secondly, we analyzed the prevalence of FI in different age groups (Table 2). Overall 7.9% (95% CI, 6.4–9.4) of the respondents suffered from FI. There was no statistically significant difference in the prevalence of FI between males and females ($P = .998$), nor between the age groups ($P = .114$). We did, however, notice a slight decrease in the prevalence of FI

Table 2
Prevalences of constipation and fecal incontinence in the Dutch population

		Constipation			Fecal incontinence			Constipation & Fecal incontinence		
	Total n	%	95% CI	*P* value	%	95% CI	*P* value	%	95% CI	*P* value
Overall	1259	24.5	22.1–26.8		7.9	6.4–9.4		3.5	2.5–4.5	
Gender				< .001			NS			NS
Male	579	18.8	15.6–22.0		7.9	5.7–10.2		3.6	2.1–5.2	
Female	680	29.3	25.8–32.7		7.9	5.9–10.0		3.4	2.0–4.7	
Age (years)				< .001			NS			.004
18-34	273	36.3	30.5–42.0		11.0	7.3–14.7		7.0	3.9–10.0	
35-46	256	26.6	21.1–32.0		9.0	5.5–12.5		3.9	1.5–6.3	
47-55	253	19.0	14.1–23.8		5.5	2.7–8.4		2.0	0.2–3.7	
56-64	234	19.2	14.1–24.3		8.1	4.6–11.6		1.3	-0.2–2.7	
65-85	243	19.8	14.7–24.8		5.8	2.8–8.7		2.9	0.8–5.0	

with increasing age in the younger age groups (Table 2). Thus, we also analyzed whether the probability of FI changed with age (Figure 1B). We found that the overall probability of FI did not change significantly with increasing age.

Co-occurrence of constipation and fecal incontinence

Lastly, we analyzed the prevalence of the co-occurrence of constipation and FI in the different age groups (Table 2). We found that 3.5% (95% CI, 2.5–4.5) of the respondents suffered from both disorders. Moreover, we observed that the two disorders co-occurred significantly more often in the younger age groups, namely 7.0% (95% CI, 3.9–10.0) in the 18 to 34-year-olds versus 2.9% (95% CI, 0.8–5.0) in the 65 to 85-year-olds (P = .004, Table 2). In addition, we found that constipated respondents were 2.7 times more likely to suffer from FI than non-constipated respondents (95% CI, 1.8–4.0) (Table 3). Nearly three-quarters of the respondents, *i.e.* 71.1% (n = 895), experienced neither constipation nor FI.

We also analyzed which types of FI (soiling, solid stool, urge, and liquid stool) were suffered by respondents with constipation (Table 3). All types of FI were seen significantly

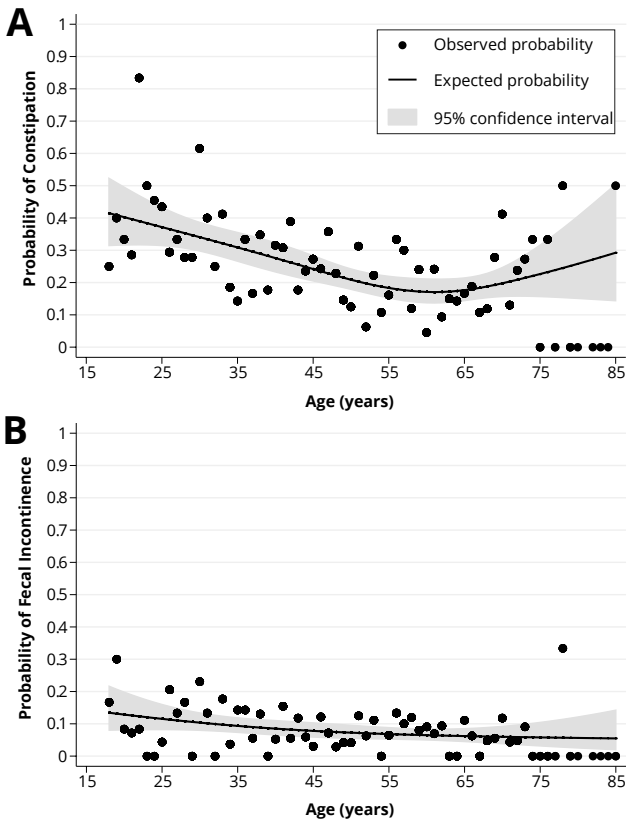

Figure 1
The probability of constipation and fecal incontinence plotted against the age of the respondents.
A: The probability of constipation gradually decreased to a minimum value of approximately 0.17 at 61 years, after which the probability increased as respondents' ages increased.
B: The overall probability of FI did not change with increasing respondents' age.

Table 3
Types of fecal incontinence in respondents with constipation

	Constipation		
	No	Yes	
	No. (%)	No. (%)	*P* value
Overall	951 (100.0)	308 (100.0)	
Fecal incontinence	56 (5.9)	44 (14.3)	< .001
Types of fecal incontinence[a]			
Soiling	45 (4.7)	34 (11.0)	< .001
Solid stool	11 (1.2)	25 (8.1)	< .001
Urge	19 (2.0)	22 (7.1)	< .001
Liquid stool	16 (1.7)	22 (7.1)	< .001

[a] Respondents often suffered from multiple types of fecal incontinence

Table 4
Constipation complaints in respondents with fecal incontinence

	Fecal incontinence		
	No	Yes	
	No. (%)	No. (%)	*P* value
Overall	1159 (100.0)	100 (100.0)	
Constipation	264 (22.8)	44 (44.0)	< .001
Constipation complaints			
Straining	333 (28.7)	50 (50.0)	< .001
Lumpy or hard stools	436 (37.6)	40 (40.0)	NS
Incomplete evacuation	278 (24.0)	54 (54.0)	< .001
Anorectal blockage	180 (15.5)	36 (36.0)	< .001
Manual maneuvers	86 (7.4)	25 (25.0)	< .001
Fewer than three bowel movements per week	89 (7.7)	25 (25.0)	< .001
Laxative usage at least multiple times per month	62 (5.3)	23 (23.0)	< .001

more often in constipated respondents than in respondents who did not suffer from constipation (P < .001). Subsequently, we analyzed the prevalence of the different constipation complaints incorporated in the Rome III criteria for constipation and compared respondents with and without FI (Table 4). Straining and incomplete evacuation were the constipation complaints most frequently experienced by respondents with FI, namely by 50.0% (50 out of 100) and 54.0% (54 out of 100), respectively. Manual maneuvers and reduced stool frequency were experienced least, namely by 25.0% (25 out of 100) and 25.0% (25 out of 100) respondents, respectively. Nearly all the constipation complaints analyzed, except lumpy or hard stools, were seen significantly more often in respondents who suffered from FI than in respondents who did not suffer from FI (P < .001, Table 4).

Moreover, we analyzed the prevalence of laxative use in respondents with constipation, FI, or both. We found that the use of laxatives, at least several times per month, was significantly higher in patients in whom constipation and FI co-occurred (43.2%) when compared to those with only constipation (21.4%, P = .002) or FI (23.0%, P = .014).

Defecation frequency and stool consistency

We also investigated defecation frequency (Figure 2A) and stool consistency (Figure 2B) in patients with no defecation disorder, constipation, FI, and in whom constipation and FI co-occurred.

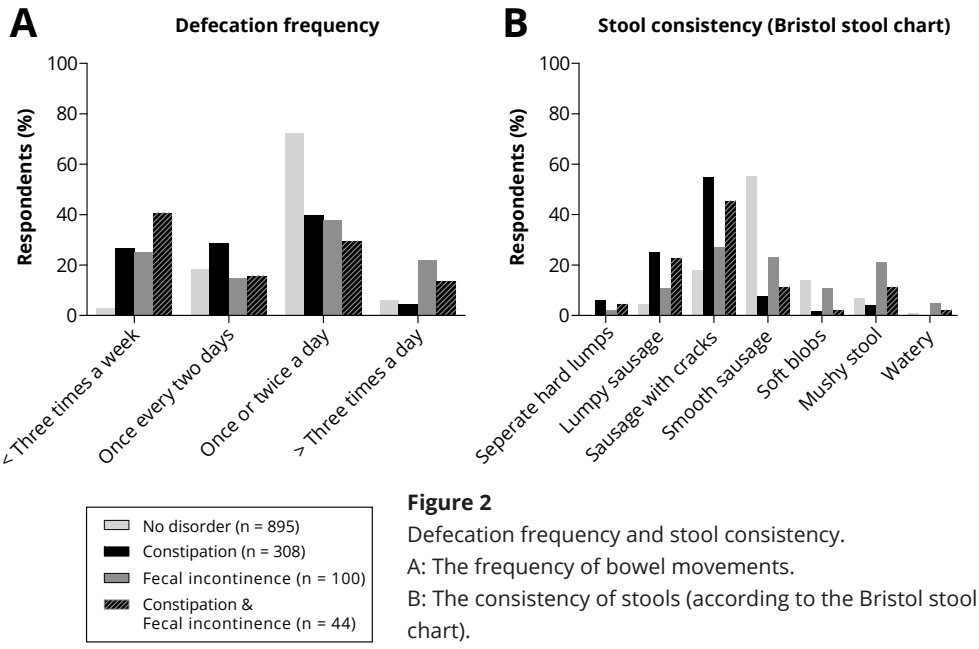

Figure 2
Defecation frequency and stool consistency.
A: The frequency of bowel movements.
B: The consistency of stools (according to the Bristol stool chart).

The respondents who suffered from constipation (n = 308) had a significantly lower defecation frequency than the respondents with no defecation disorder ($P < .001$, Figure 2A). Only 26.6% of the respondents with constipation had less than three bowel movements per week, while the defecation frequency of the majority (68.8%) was normal, *i.e.* every other day to twice a day.

Respondents with FI (n = 100) were more likely to have either a low frequency or a high frequency of bowel movements (25.0% and 22.0%, respectively) than respondents with no defecation disorder (2.8% and 6.1%, respectively, $P < .001$). Even so, the defecation frequency of the majority (53.0%) of the respondents with FI was normal.

Interestingly, of the respondents in whom constipation and FI co-occurred (n = 44), a large portion (40.9%) had a low frequency of bowel movements (less than three per week), which was significantly different to the group of respondents with no defecation disorder (2.8%, $P < .001$).

We also investigated stool consistency according to the Bristol stool chart (Figure 2B). Overall, stool consistency of constipated respondents was harder than that of respondents with no defecation disorder ($P < .001$). Even so, the majority (62.7%) of respondents who suffered from constipation had a normal stool consistency. Respondents who suffered FI had either very hard or very soft (watery) stools (13.0% and 37.0%, respectively) more often than respondents with no defecation disorder (4.5% and 22.0%, respectively, $P < .001$). Nevertheless, stool consistency of the majority (50.0%) of the respondents who suffered FI was normal. Lastly, we found that respondents who suffered from both constipation and FI had a hard stool consistency (27.3%) more often than respondents with no defecation disorder (4.5%, $P < .001$).

Respondents' qualification of bowel habits and help-seeking behavior

At the beginning of the questionnaire we asked respondents how they would qualify their ability to hold and pass stools. The answer of 17.6% (n = 221) of the respondents was "very good", 48.3% (n = 608) answered with "good", 27.4% (n = 345) with "reasonable", 6.0% (n = 76) with "poor", and the answer given by 0.7% (n = 9) was "very poor". Additionally, we analyzed these answers for the subgroups of respondents with no defecation disorder, constipation, FI, and for those respondents in whom constipation and FI co-occurred (Figure 3A). On average, respondents with either constipation, FI, or both, rated their bowel habits significantly lower than the group without a defecation disorder ($P < .001$). Nevertheless, 48.7% (150 out of 308) of the respondents with constipation, 35.0% (35 out of 100) of those with FI, and 38.6% (17 out of 44) of those with co-occurring constipation and FI rated their ability to hold and pass stools as either "good" or "very good".

Furthermore, we also asked respondents if they ever discussed their constipation or

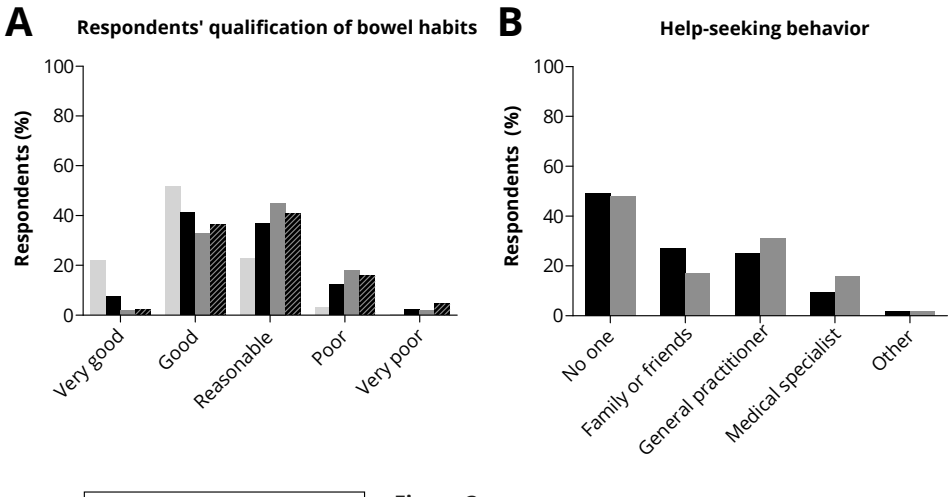

Figure 3
Opinion on bowel habits and help-seeking behavior.
A: Respondents' qualification of own bowel habits regarding the ability to hold and pass stools.
B: With whom respondents discussed their defecation disorders.

FI problems with anyone, and if so, who did they speak to (Figure 3B). Of all constipated respondents, 49.4% (152 out of 308) had never spoken to anyone about their constipation problems. For FI, we found that 48.0% (48 out of 100) had never mentioned their incontinence complaints to anyone.

Defecation disorders in "healthy" respondents

We also performed an analysis in a "healthy" subgroup (n = 1008), *i.e.* respondents without a history of bowel surgery or somatic disorders that could potentially influence their bowels. The prevalence of constipation in the group of "healthy" respondents was 22.3% (95% CI, 19.7–24.9), and not significantly different from the total group investigated, which was 24.5% (95% CI, 22.1–26.8; $P = .232$). By contrast, there was a significant difference in the prevalence of FI between the "healthy" subgroup and the total group, 5.5% (95% CI, 4.1–6.9) versus 7.9% (95% CI, 6.4–9.4; $P = .020$), respectively. The co-occurrence of constipation and FI was significantly lower in the "healthy" subgroup (1.9%; 95% CI, 1.0–2.7), than in the total group (3.5%; 95% CI, 2.5–4.5; $P = .020$). While the prevalence of constipation, FI, and the combination of both disorders was higher in respondents with a history of bowel surgery and somatic disorders, there was no significant difference between respondents who had a history of bowel surgery and respondents who had a somatic disorder.

DISCUSSION

This nationwide Dutch survey was the first study on the prevalence of constipation, FI, and the co-occurrence of these two disorders using the Groningen DeFeC questionnaires. We demonstrated that both constipation and FI occurred frequently in the Dutch population, with a prevalence of 24.5% and 7.9%, respectively. More importantly, we showed that in 3.5% of the population the disorders co-occurred, and that constipated individuals were more likely to suffer from FI.

Even though constipation and FI have been studied extensively in the general population, studies on the co-occurrence of the two disorders are limited to pediatric and geriatric populations and to women who visited gynecologic clinics.[12,16] In the general adult population, studies only pointed out that certain symptoms of constipation, such as incomplete evacuation, are risk factors for FI.[12] Our study, however, demonstrated that 3.5% of the general Dutch population suffered from both constipation and FI. This co-occurrence of disorders is seen particularly in 18 to 34-year-old males and females. The relationship between these two disorders could indicate that constipation is a risk factor for FI and that it might play a role in the pathophysiology of FI. This theory is supported by our finding that constipated respondents suffered from FI more often than non-constipated respondents. Furthermore, this theory could also help explain the relatively high prevalence of FI we found in the younger age groups, who suffered from constipation significantly more often than the older age groups.

Three mechanisms have been described as possible causes for the co-occurrence of constipation and FI.[12] Firstly, it is known that in pediatric and geriatric populations constipation can lead to overflow FI. Secondly, excessive straining, associated with constipation, can lead to pelvic floor denervation and weakness, which could eventually result in FI. Thirdly, rectal evacuatory disorders, such as dyssynergic defecation and rectocele, can lead to incomplete rectal evacuation, resulting in post-defecation leakage. These mechanisms are supported by our results, as we found that respondents with FI suffered from straining and incomplete evacuation complaints significantly more often than respondents without FI. Nevertheless, it is important to perform follow-up studies to elucidate the mechanisms underlying the co-occurrence of constipation and FI in the general population.

Interestingly, when we investigated the defecation frequency and stool consistency of respondents with different defecation disorders, we found that the majority of respondents with a bowel disorder had a normal defecation frequency and stool consistency. This indicates that frequency and consistency are poor predictors of the presence of constipation or FI and are of little value without the addition of more in-depth

questions on defecation habits. Additionally, we found that a large portion of respondents who suffered from both constipation and FI had low defecation frequencies (less than three times per week), while this was not the case in respondents who only suffered from constipation. Moreover, respondents in whom constipation and FI co-occurred used significantly more laxatives than those who suffered from either constipation or FI. Since the group of respondents in whom the two disorders co-occurred also suffered significantly more often from other constipation-associated complaints, we hypothesize that this group suffered from a more severe form of constipation.

When asked to comment on their bowel habits, respondents with constipation, FI, or co-occurrence of both disorders qualified their ability to hold and pass stools significantly lower than respondents without a defecation disorder. Nevertheless, 48.7% of the respondents with constipation, 35.0% of those with FI, and 38.6% of those in whom the two disorders co-occurred qualified their ability to hold and pass stools as either "good" or "very good". Possibly, a considerable part of the population is unaware as to what is considered normal, or abnormal, regarding their own bowel habits or they have become used to the abnormal bowel condition and do, therefore, not recognize it as being a problem. Another interesting finding for patients who suffered either constipation or FI was that 49.4% and 48.0%, respectively, never discussed their defecation problems with anyone. Reasons for these high percentages could be unawareness of the problem and possible treatment options, embarrassment, or even ignorance.[17–20] Since there are good treatment possibilities for constipation and FI, it would seem justified for general practitioners to pay more attention to defecation disorders, even if this is not the primary reason for being consulted.

We found a prevalence of 24.5% for constipation. This is relatively high in comparison to previous Rome II or Rome III criteria-based studies that reported prevalences varying between 2.5 and 22.8%.[2–9] These discrepancies might result from different demographic and geographical features of the populations investigated, such as age and gender distribution, and a variation in diet. Moreover, although it was previously reported that FI increases with age, our study did not confirm this findings, for which we offer two explanations. Firstly, we used a digital survey system and, therefore, we possibly included a selection of relatively healthy elderly respondents. Secondly, and more importantly, the relatively high prevalence of FI in the younger age groups could have resulted from the significantly higher prevalence of the co-occurrence of constipation and FI in these groups in comparison to the older age groups. Based on daily experience you would expect that the severity of FI indeed increases as people get older and this is something that we plan to investigate in future studies.

To investigate whether defecation disorders were predominantly caused by

comorbidities, we performed a subanalysis. On the one hand, we found that the prevalence of FI was significantly lower in the "healthy" subgroup, *i.e.* respondents without a history of bowel surgery or somatic disorders, than in the total study group. On the other hand, we found no significant difference regarding the prevalence of constipation when comparing the "healthy" subgroup to the total population. Thus, it would seem that somatic disorders and bowel surgery might constitute considerably larger risk factors for developing FI than for developing constipation.

The main limitation of this study was the possible selection bias towards healthy elderly respondents by performing a digital survey. It is most likely, therefore, that as far as the elderly are concerned, our study underestimated the prevalence of constipation, and more importantly the prevalence of FI. On the other hand, by performing this survey digitally, we were able to include a large and representative group of the Dutch population reflecting the gender and age proportions as found in the overall population. Furthermore, a response rate of 54% may be considered low. This might be explained by the subject and length of the questionnaire. This low response rate could, however, also have biased the results.

Conclusions

In accordance with our hypothesis, we found that a relatively large part of the Dutch population suffered from both constipation and FI. Moreover, even young and healthy respondents often suffered from defecation disorders. The increased likelihood of FI in constipated respondents leads us to conclude that constipation could be considered a causative factor of FI. We, therefore, recommend that patients seeking medical attention for either constipation or FI should be examined for both disorders, since they often co-occur. Remarkably, a large part of the population was unaware of the fact that their bowel habits could not to be considered normal, and a significant number of these respondents had never sought medical attention. These findings warrant further investigations in order to improve patient awareness and healthcare for constipation and FI.

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REFERENCES

1 Bartlett L, Nowak M, Ho YH. Reasons for non-disclosure of faecal incontinence: a comparison between two survey methods. Tech Coloproctol. 2007;11:251–7.

2 Lu CL, Chang FY, Chen CY, et al. Significance of Rome II-defined functional constipation in Taiwan and comparison with constipation-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2006;24:429–38.

3 Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. Aliment Pharmacol Ther. 2007;25:599–608.

4 Pourhoseingholi MA, Kaboli SA, Pourhoseingholi A, et al. Obesity and functional constipation; a community-based study in Iran. J Gastrointestin Liver Dis. 2009;18:151–5.

5 Papatheodoridis G V, Vlachogiannakos J, Karaitianos I, et al. A Greek survey of community prevalence and characteristics of constipation. Eur J Gastroenterol Hepatol. 2010;22:354–60.

6 Cottone C, Tosetti C, Disclafani G, et al. Clinical features of constipation in general practice in Italy. United Eur Gastroenterol J. 2014;2:232–8.

7 Heidelbaugh JJ, Stelwagon M, Miller SA, et al. The spectrum of constipation-predominant irritable bowel syndrome and chronic idiopathic constipation: US survey assessing symptoms, care seeking, and disease burden. Am J Gastroenterol. 2015;110:580–7.

8 Boyce PM, Talley NJ, Burke C, et al. Epidemiology of the functional gastrointestinal disorders diagnosed according to Rome II criteria: an Australian population-based study. Intern Med J. 2006;36:28–36.

9 Ng KS, Nassar N, Hamd K, et al. Prevalence of functional bowel disorders and faecal incontinence: an Australian primary care survey. Colorectal Dis. 2015;17:150–9.

10 Melville JL, Fan M-Y, Newton K, et al. Fecal incontinence in US women: A population-based study. Am J Obstet Gynecol. 2005;193:2071–6.

11 Bharucha AE, Zinsmeister AR, Locke GR, et al. Prevalence and burden of fecal incontinence: A population-based study in women. Gastroenterology. 2005;129:42–9.

12 Nurko S, Scott SM. Coexistence of constipation and incontinence in children and adults. Best Pract Res Clin Gastroenterol. 2011;25:29–41.

13 Statistics Netherlands (2015) Population key figures. http://www.cbs.nl/en-GB/menu/cijfers/kerncijfers/default.htm. Accessed 16 November 2015

14 Longstreth G, Thompson G, Chey W, et al. Functional Bowel Disorders. Gastroenterology. 2006;130:1480–91.

15 Bharucha, A. E., Wald, A., Enck, P. & RS. Functional anorectal disorders. Gastroenterology. 2006;130:1510–8.

16 Sze EH, Barker CD, Hobbs G. A cross-sectional survey of the relationship between fecal incontinence and constipation. Int Urogynecol J. 2013;24:61–5.

17 Pare P, Ferrazzi S, Thompson WG, et al. An epidemiological survey of constipation in canada: definitions, rates, demographics, and predictors of health care seeking. Am J Gastroenterol. 2001;96:3130–7.

18 Rizk DE, Hassan MY, Shaheen H, et al. The prevalence and determinants of health care-seeking behavior for fecal incontinence in multiparous United Arab Emirates females. Dis Colon Rectum. 2001;44:1850–6.

19 Cheng C, Chan AO, Hui WM, et al. Coping strategies, illness perception, anxiety and depression of patients with idiopathic constipation: a population-based study. Aliment Pharmacol Ther.

2003;18:319–26.
20 Bharucha AE, Dunivan G, Goode PS, et al. Epidemiology, pathophysiology, and classification of fecal incontinence: state of the science summary for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop. Am J Gastroenterol. 2015;110:127–36.

PART III

Long-term outcomes of Hirschsprung's disease

CHAPTER 8

Long-term functional outcomes and quality of life in patients with Hirschsprung's disease

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SUMMARY

Background

It is unclear whether functional outcomes improve or deteriorate with age following surgery for Hirschsprung's disease (HD). Our aim was to determine the long-term functional outcomes and quality of life (QoL) in patients with HD by performing a cross-sectional study.

Methods

Patients with pathologically proven HD older than eight years were included. Patients with a permanent stoma or intellectual disability were excluded. Functional outcomes were assessed by Rome IV criteria using the Defecation and Fecal Continence (DeFeC) questionnaire. QoL was assessed by the CHQ-CF87 questionnaire or by the WHOQOL-100 questionnaire. Reference data of healthy controls were available for comparison.

Results

Of 619 patients invited, 55.9% responded (n = 346, median age 18 years, range 8–45). The prevalence of constipation was comparable in pediatric and adult patients (22.0% versus 22.0%) and in patients and controls. Compared to controls, adult patients suffered significantly more often from straining (50.3% versus 36.1%, $P = .011$) and incomplete evacuation (47.4% versus 27.2%, $P < .001$). The prevalence of fecal incontinence, most commonly soiling, was lower in adult patients compared to pediatric patients (16.8% versus 37.6%, $P < .001$), but remained higher than in controls (16.8% versus 6.1%, $P = .003$). Patients with poor functional outcomes scored significantly lower in several QoL domains.

Conclusions

This study has shown that functional outcomes are better in adult patients compared to pediatric patients, but symptoms of constipation and soiling persist in a substantial group of adult HD patients. The persistence of defecation problems are an indication that continuous care is necessary in this specific group of patients.

INTRODUCTION

Hirschsprung's disease (HD) is a congenital absence of ganglion cells of the distal bowel that in most cases presents with severe functional obstruction shortly after birth. Following diagnosis, resection is usually performed to remove the aganglionic bowel and to restore continuity. While many patients may attain normal bowel function following surgery, defecation disorders, such as constipation or fecal incontinence, can persist.[1–11]

It has been postulated that functional outcomes improve as patients grow older, especially after reaching adolescence.[5–7] Other studies, however, have drawn attention to the fact that long-term outcomes of HD in adulthood are far from satisfactory.[2–4] Indeed, one of these studies found that defecation problems actually deteriorated after the patients reached adulthood[3]. Unfortunately, a lack of data on healthy controls hinders interpretation of the majority of these studies.

Persistent defecation disorders, such as constipation and fecal incontinence, can potentially have a negative influence on quality of life (QoL).[12,13] A distinction is often made between generic QoL and health-related QoL, the latter focusing primarily on aspects of life that are directly influenced by an individual's health. In patients with HD the relationship between functional complaints and QoL has been studied previously, but these studies were often performed with health-related QoL questionnaires and only rarely were generic QoL questionnaires used.[14] Moreover, it remains unclear how functional outcomes continue to influence QoL after the transition into adulthood.[14]

The primary aim of this study was to investigate the long-term functional outcomes in different age groups and to compare them with matched controls. Secondarily, we aimed to identify factors associated with poor outcomes and to evaluate the influence of poor functional outcomes on QoL using generic QoL questionnaires.

METHODS

Study design

We reviewed the medical records of all known patients diagnosed with HD in all six pediatric surgical centers in the Netherlands. Inclusion criteria were pathologically proven HD and a minimum age of eight years. The following variables were collected from the records: comorbidities, length of aganglionosis, surgical treatment, episodes of enterocolitis, surgical complications, and additional surgical interventions. Enterocolitis was defined as the presence of symptoms such as abdominal distension, diarrhea, bloody stools, and/or fever with the intention-to-treat as such.[15] Surgical complications were defined as complications that occurred within 30 days and that were the direct result of

the initial surgical intervention (eg, anastomotic leakage, wound infection, adhesions).

Following the exclusion of patients who were ineligible for participation (eg, deceased, lived abroad, had a permanent stoma or an intellectual disability), we invited the remaining patients to participate in our study. In case of pediatric patients between 8 to 17 years we asked the parents or caregivers to participate together with the patients, or on their behalf. Upon agreeing to participate, patients received questionnaires on anorectal functioning and QoL. For pediatric patients this entailed the Pediatric Defecation and Fecal Continence (P-DeFeC, see Appendices) questionnaire[16] and the Child Health Questionnaire Child Form (CHQ-CF87).[17] Adult patients received the Defecation and Fecal Continence (DeFeC, see Appendices) questionnaire[16] and the World Health Organization Quality of Life (WHOQOL-100) questionnaire.[18]

Medical ethical approval was obtained for the study and written informed consent was collected of each participant.

Assessment of functional outcomes

The functional outcomes were assessed using patients' answers on the P-DeFeC and DeFeC questionnaires, which allowed us to score Rome IV criteria and assess the use of therapies for constipation and fecal incontinence.

Constipation was defined by the Rome IV criteria for functional constipation.[19] To meet these criteria patients should have at least two of the following symptoms: straining, hard or lumpy stools, incomplete evacuation, anorectal obstruction, manual maneuvers to facilitate defecation, or fewer than three bowel movements a week. Additionally, loose stools should rarely be present without the use of laxatives. Additionally, we assessed the individual symptoms incorporated in the Rome IV criteria for functional constipation that had to occur at least several times a month. Fecal incontinence was defined by the Rome IV criteria for fecal incontinence, ie, recurrent uncontrolled passage of fecal material, including soiling, at least several times a month.[20] Additionally, we assessed several subtypes of fecal incontinence, such as, soiling (ie, the loss of small amounts of feces), urge incontinence (ie, inability to reach the toilet in time), incontinence for solid stool (ie, loss of large amounts of solid feces without having felt urge), and incontinence for liquid stool (ie, loss of watery stools or diarrhea).

By means of the questionnaire we also evaluated the use of laxatives and bowel management at least several times a month as therapy for constipation or fecal incontinence.

Reference data for the P-DeFeC and DeFeC questionnaires were available from studies that had previously been performed in the general Dutch population. This produced 1103 healthy children and adults who did not have a history of bowel surgery and who did not

suffer from somatic diseases that could influence their bowels.[21,22]

Assessment of quality of life

In pediatric patients aged 8 to 17 years QoL was assessed using the CHQ-CF87.[17] The CHQ-CF87 is a generic QoL questionnaire with 87 items that are scored on a four to six-point Likert scale. Following completion, ten multi-item domains and two single-item questions were calculated and converted to a 0-100 point continuum, whereby a higher score indicates better QoL. For our current study we assessed the following domains: behavior, mental health, self-esteem, and general health.

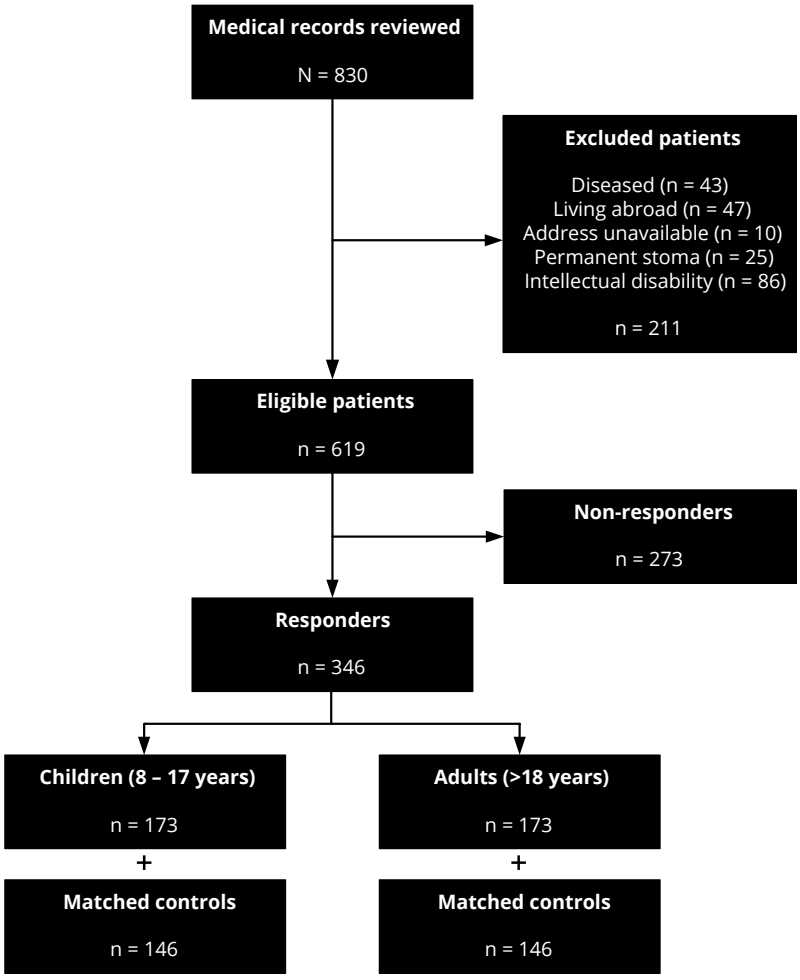

Figure 1
Study flow diagram

In adult patients we assessed QoL using the WHOQOL-100.[18] The WHOQOL-100 consists of 100 items covering six domains and a general evaluative facet (overall QoL and general health). The items are scored on a five-point Likert scale. Calculated domain scores range between 4 and 20 points, whereby a higher domain score indicates better QoL. For our current study we used the following domains: overall QoL, physical health, psychological health, and social relationships.

Reference data of the healthy Dutch population were available for both CHQ-CF87[23] and WHOQOL-100 questionnaires (with courtesy of Dr. J. de Vries, University of Tilburg).[24]

Statistical analysis

Data were analysed with SPSS 23.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Proportions were reported as prevalence percentages with 95% confidence intervals (CIs). Quantitative variables were either reported as means with SDs or as medians with ranges. Statistical tests were limited to the chi-square, Mann-Whitney, and t tests. Univariate and multivariate logistic regression analyses were used to test the association of potential risk factors with the likelihood of fecal incontinence and were reported as odds ratios (ORs) with 95% CIs. The multivariate analysis was built using variables that tended towards significance ($P < .100$) in the univariate analyses. Two-sided P values of less than .050 were considered statistically significant.

RESULTS

Patient characteristics and drop-out analysis

Based on our inclusion criteria we identified 830 patients eligible for inclusion. We excluded 211 patients who had died (n = 43), who lived abroad (n = 47), whose addresses were unavailable (n = 10), or who were unable to complete one of the questionnaires because of a permanent stoma (n = 25) or intellectual disability (eg, Down syndrome, n = 86). The most common reasons for a permanent stoma were postoperative complications (n = 7), persistent constipation (n = 5), and severe intellectual disability (n = 3). Thus, a total of 619 patients received an invitation to participate in our study (Figure 1).

Following invitation, 55.9% (n = 346) of patients and their parents or caregivers agreed and completed the questionnaires (Table 1). These 346 patients consisted of 173 pediatric patients aged 8 to 17 years and 173 adult patients. Additional patient characteristics are listed in Table 1. The drop-out analysis only showed a significant difference in median age between non-responders and responders (22 years, range 8–50, versus 18 years, range 8–45, respectively, $P = 0.004$, Table 1). The patients who responded (n = 346) were randomly matched 1:1 with the controls on sex and age. Because of the high prevalence

Table 1
Patient characteristics and drop-out analysis

	Non-responders No. (%)	Responders No. (%)	*P* value
Overall	273 (100.0)	346 (100.0)	
Sex			.373
Men	224 (82.1)	274 (79.2)	
Women	49 (17.9)	72 (20.8)	
Age (years, median, range)	22 (8 – 50)	18 (8 – 45)	.004
Comorbidities	26 (9.5)	33 (9.5)	.999
Length of aganglionosis			.804
Ultrashort	5 (1.8)	10 (2.9)	
Rectosigmoid	222 (81.3)	282 (81.5)	
Long segment	23 (8.4)	29 (8.4)	
Total colonic	23 (8.4)	25 (7.2)	
Preoperative enterocolitis	30 (11.0)	46 (13.3)	.395
Primary surgical treatment			.443
Surgical reconstruction	265 (97.1)	337 (97.4)	
Sphincterectomy	3 (1.1)	4 (1.2)	
Other	2 (0.7)	0 (0.0)	
None/conservative	3 (1.1)	5 (1.4)	
Surgical reconstructions			.166
Duhamel	149 (56.2)	210 (62.3)	
Soave	1 (0.4)	1 (0.3)	
Rehbein	80 (30.2)	73 (21.7)	
Swenson	0 (0.0)	1 (0.3)	
Transanal endorectal pull-through	35 (13.2)	52 (15.4)	
Postoperative complication	26 of 270 (9.6)	36 of 341 (10.6)	.706
Postoperative enterocolitis	24 of 270 (8.9)	47 of 341 (13.8)	.061
Redo pull-through	15 of 270 (5.6)	23 of 341 (6.7)	.546

of male patients, we were unable to match 52 patients to appropriate controls. This did not result in significant differences in sex or age between the group of HD patients (n = 346) and the control group (n = 294).

Functional outcomes in pediatric patients

The prevalence of constipation was comparable between pediatric patients and their controls (22.0% versus 14.3%, respectively). Nevertheless, pediatric patients suffered from symptoms, such as, straining, incomplete evacuation, and anorectal obstruction significantly more often (Table 2). Compared to controls, pediatric patients used laxatives

(30.6% versus 4.1%, $P < .001$) and bowel management (17.9% versus 0.7%, $P < .001$) to treat constipation significantly more often.

The overall prevalence of fecal incontinence was significantly higher in pediatric patients compared to pediatric controls (37.6% versus 6.1%, $P < .001$). The most common subtype of fecal incontinence in pediatric patients was soiling (34.7%), followed by incontinence for solid stool (6.9%) and liquid stool (8.7%), which were all significantly more prevalent compared to controls (Table 2). Lastly, 11.0% of the pediatric patients used bowel management to treat fecal incontinence, whereas this was merely 0.7% in controls ($P < .001$).

Functional outcomes in adult patients

The prevalence of constipation was comparable between adult patients and adult controls (22.0% versus 19.0%, $P = .520$). Compared to controls, adult patients suffered from symptoms, such as straining and incomplete evacuation, significantly more often (Table 2). Using laxatives was not significantly higher in adult patients compared to their control group, whereas they did retain a higher prevalence of bowel management to treat constipation (8.1% versus 0.7%, $P = .002$, Table 2).

The overall prevalence of fecal incontinence remained significantly higher in adult patients compared to their controls (16.8% versus 6.1%, $P = .003$). This was mainly the result of a significantly higher prevalence of soiling (16.8% versus 4.1%, $P < .001$), which was the only significant difference in subtypes of fecal incontinence (Table 2).

Comparison of functional outcomes in pediatric and adult patients

The prevalence of constipation between pediatric and adult patients was equal (22.0% versus 22.0%). Nevertheless, in comparison to pediatric patients, adult patients reported straining and manual maneuvers when defecating more often (Table 2). For the treatment of constipation, pediatric patients used laxatives (30.6% versus 5.2%, $P < .001$) and bowel management (17.9% versus 8.1%, $P = .007$) significantly more often than adult patients.

The overall prevalence of fecal incontinence was lower in adult patients compared to pediatric patients (16.8% versus 37.6%, $P < .001$). The subtypes of fecal incontinence, such as, soiling, incontinence for solid stool, and incontinence for liquid stool were all significantly less prevalent in adult patients compared to pediatric patients (Table 2). Lastly, only 1.7% of the adult patients required bowel management for their fecal incontinence, compared to 11.0% of pediatric patients ($P = .017$).

Table 2
Functional outcomes in pediatric and adult patients

	Children (8 – 17 years)			Adults (> 18 years)			Children vs. adults
	Patients	Controls		Patients	Controls		Patients
	No. (%)	No. (%)	*P* value	No. (%)	No. (%)	*P* value	*P* value
Overall	173 (100.0)	147 (100.0)		173 (100.0)	147 (100.0)		
Constipation							
Prevalence of constipation (Rome IV)	38 (22.0)	21 (14.3)	.077	38 (22.0)	28 (19.0)	.520	.999
Constipation symptoms							
Straining	64 (37.0)	32 (21.8)	.003	87 (50.3)	53 (36.1)	.011	.013
Lumpy or hard stools	5 (2.9)	14 (9.5)	.012	11 (6.4)	9 (6.1)	.931	.125
Incomplete evacuation	68 (39.3)	13 (8.8)	< .001	82 (47.4)	40 (27.2)	< .001	.129
Anorectal obstruction	39 (22.5)	17 (11.6)	.010	44 (25.4)	25 (17.0)	.068	.529
Manual maneuvers	0 (0)	3 (2.0)	.059	10 (5.8)	7 (4.8)	.686	.001
Fewer than three bowel movements per week	12 (6.9)	12 (8.2)	.678	18 (10.4)	19 (12.9)	.482	.252
Laxative usage	53 (30.6)	6 (4.1)	< .001	9 (5.2)	6 (4.1)	.636	< .001
Bowel management for constipation	31 (17.9)	1 (0.7)	< .001	14 (8.1)	1 (0.7)	.002	.007
Fecal incontinence							
Prevalence of fecal incontinence (Rome IV)	65 (37.6)	9 (6.1)	< .001	29 (16.8)	9 (6.1)	.003	< .001
Subtypes of fecal incontinence*							
Soiling	60 (34.7)	6 (4.1)	< .001	29 (16.8)	6 (4.1)	< .001	< .001
Urge incontinence	7 (4.0)	2 (1.4)	.148	2 (1.2)	3 (2.0)	.525	.091
Incontinence for solid stool	12 (6.9)	3 (2.0)	.039	2 (1.2)	3 (2.0)	.525	.006
Incontinence for liquid stool	15 (8.7)	2 (1.4)	.004	5 (2.9)	5 (3.4)	.793	.021
Bowel management for fecal incontinence	19 (11.0)	1 (0.7)	< .001	3 (1.7)	0 (0.0)	.109	.017

* Respondents often suffered from various types of fecal incontinence

Factors associated with fecal incontinence

In the univariate analyses sex, length of aganglionosis, and postoperative complication were not significantly associated with fecal incontinence, whereas age group and redo pull-through procedures were significantly associated with fecal incontinence (Table 3). The multivariate analysis showed that adult patients were significantly less likely to report fecal incontinence than pediatric patients (OR 0.38; 95% CI, 0.21–0.66). Patients who required a redo pull-through were significantly more likely to suffer from fecal incontinence (OR 3.30; 95% CI, 1.31–8.48), compared to patients who had only undergone one procedure. There was no significant interaction between the variables.

Comparison of functional outcomes and quality of life

The QoL questionnaires were completed by 150 pediatric patients and 160 adult patients, because 36 patients omitted the QoL questionnaire after completing the questionnaire on anorectal functioning.

We first compared the mean QoL domain scores of both pediatric and adult patients to reference data of the general population (Figure 2). Pediatric patients had significantly lower scores on behavior (81 versus 85, $P < .001$), self-esteem (76 versus 79, $P = .008$), and general health (73 versus 82, $P < .001$), compared to the reference data (Figure 2A). Compared to their respective reference data set, adult patients had significantly higher scores on overall QoL (16 versus 15, $P = .001$), physical health (16 versus 15, $P = .002$), psychological health (16 versus 15, $P < .001$), and social relationships (16 versus 15, $P = .002$) (Figure 2B).

Subsequently, we analyzed how the presence of constipation and fecal incontinence resulted in different QoL domain scores (Table 4). In pediatric patients, the constipated group had significantly lower median scores on all four the domains tested compared to the non-constipated group (Table 4). Pediatric patients with fecal incontinence only had significantly lower scores on the domains behavior (83 versus 77, $P = .010$) and general health (81 versus 74, $P = .017$), compared to pediatric patients without fecal incontinence. The only significant difference between constipated and non-constipated adult patients was in the domain psychological health (16 versus 15, $P = .025$). Lastly, the only significant difference between continent and fecally incontinent adult patients was in the domain of physical health (16 versus 15, $P = .018$).

DISCUSSION

This nationwide study shows that functional outcomes were better in adult patients compared to pediatric patients, but that defecation disorders persisted in a substantial

Table 3
Prevalence and likelihood of fecal incontinence

	Total	Prevalence of fecal incontinence			Likelihood of fecal incontinence			
					Univariate logistic regression		Multivariate logistic regression	
	No. (%)	%	95% CI	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Overall	346 (100.0)	27.2	22.5–31.9					
Sex				.175				
Men	274 (79.2)	28.8	23.4–34.2		Reference			
Women	72 (20.8)	20.8	11.2–30.4		0.65 (0.35–1.21)	.177		
Age groups				< .001				
Pediatric patients (8 – 17 years)	173 (50.0)	37.6	30.3–44.9		**Reference**		Reference	
Adult patients (>18 years)	173 (50.0)	16.8	11.1–22.4		**0.33 (0.20–0.55)**	**< .001**	0.35 (0.21–0.58)	< .001
Length of aganglionosis				.482				
Ultrashort	10 (2.9)	20.0	-10.2–50.2		0.70 (0.15–3.38)	.660		
Rectosigmoid	282 (81.5)	26.2	21.1–31.4		Reference			
Long segment	29 (8.4)	27.6	10.3–44.9		1.07 (0.45–2.52)	.876		
Total colonic	25 (7.2)	40.0	19.4–60.6		1.87 (0.81–4.35)	.144		
Postoperative complication				.777				
No	305 (89.4)	27.2	22.3–32.2		Reference			
Yes	36 (10.6)	25.0	10.1–39.9		0.89 (0.40–1.97)	.769		
Redo pull–through				.001				
No	323 (93.4)	25.1	20.3–29.8		**Reference**		Reference	
Yes	23 (6.6)	56.5	34.6–78.4		**3.88 (1.64–9.20)**	**.002**	3.54 (1.46–8.62)	.005

Boldface indicates outcomes that were significant in the univariate analyses and subsequently included in the multivariate analysis

group of adult HD patients. Moreover, patients who required a redo pull-through procedure were more likely to suffer from fecal incontinence. In this group of patients, defecation disorders, especially constipation, negatively influenced QoL domains, whereby the differences were more prominent in pediatric patients than in adult patients.

Interestingly, the prevalence of constipation in both pediatric and adult HD patients was comparable to their respective control groups. These findings warrant reflection. First, the true prevalence of constipation in the HD patients may be masked by the more frequent use of laxatives and bowel management compared to the controls. If true, this could also mean that the prevalence of constipation may decrease as the HD patients grow older, because the use of laxatives and rectal irrigations was significantly lower in the adult patients than in the pediatric patients. Second, as indicated by the increased frequency of symptoms we found in this study, it may be that both pediatric and adult patients experience more severe forms of constipation.

In contrast to the prevalence of constipation, we found the prevalence of fecal incontinence to be significantly higher in HD patients compared to controls, ie 37.6% in the pediatric patients and 16.8% in the adult patients. It is important to note, however, that pediatric patients more often suffered from severe subtypes of fecal incontinence, such as solid stool and liquid stool, whereas adult patients often reported soiling. This means that both the prevalence and severity of fecal incontinence may decrease with increasing age, whereas adult HD patients do retain a significantly higher prevalence of soiling.

Table 4
Comparison of functional outcomes and quality of life

	Constipation (Rome IV criteria)			Fecal incontinence (Rome IV criteria)		
	No	Yes		No	Yes	
Domains	Median (range)	Median (range)	*P* value	Median (range)	Median (range)	*P* value
CHQ-CF87 (n = 150)						
Behavior	82 (21 – 99)	76 (46 – 97)	.010	83 (61 – 99)	77 (21 – 98)	.010
Mental health	81 (50 – 100)	76 (42 – 97)	.021	81 (42 – 100)	77 (50 – 100)	.056
Self-esteem	77 (30 – 100)	73 (41 – 100)	.013	75 (41 – 100)	77 (30 – 100)	.877
General health	80 (21 – 100)	69 (19 – 99)	.004	81 (19 – 100)	74 (26 – 100)	.017
WHOQOL-100 (n = 160)						
Overall QoL	16 (10 – 20)	16 (7 – 20)	.055	16 (9 – 20)	16 (7 – 20)	.319
Physical health	16 (8 – 20)	15 (7 – 20)	.077	16 (10 – 20)	15 (7 – 20)	.018
Psychological health	16 (10 – 20)	15 (10 – 19)	.025	16 (10 – 20)	15 (10 – 20)	.204
Social relationships	16 (9 – 20)	15 (9 – 19)	.079	16 (9 – 20)	16 (9 – 20)	.141

In contrast to our results, a recent study by Neuvonen and colleagues concluded that fecal incontinence would eventually diminish to a prevalence not significantly different to that of the healthy controls, even though the prevalence of soiling persisted to well over 40% in their adult subgroup.[6] It therefore seems that fecal continence may improve with age, but that problems do persist well into adulthood. The persistence of impaired fecal continence could have various causes. First, fecal incontinence in these patients may result from damage to the anal sphincter during reconstructive surgery.[25] Second, impaired continence may result from more severe constipation in HD patients,[21] which could be the result of persistently absent rectoanal inhibitory reflex, stenosis of the anal sphincter following surgery, or absent pelvic floor coordination.[26] Third, the absence of a rectal reservoir following surgery and subsequent increased defecation frequency may

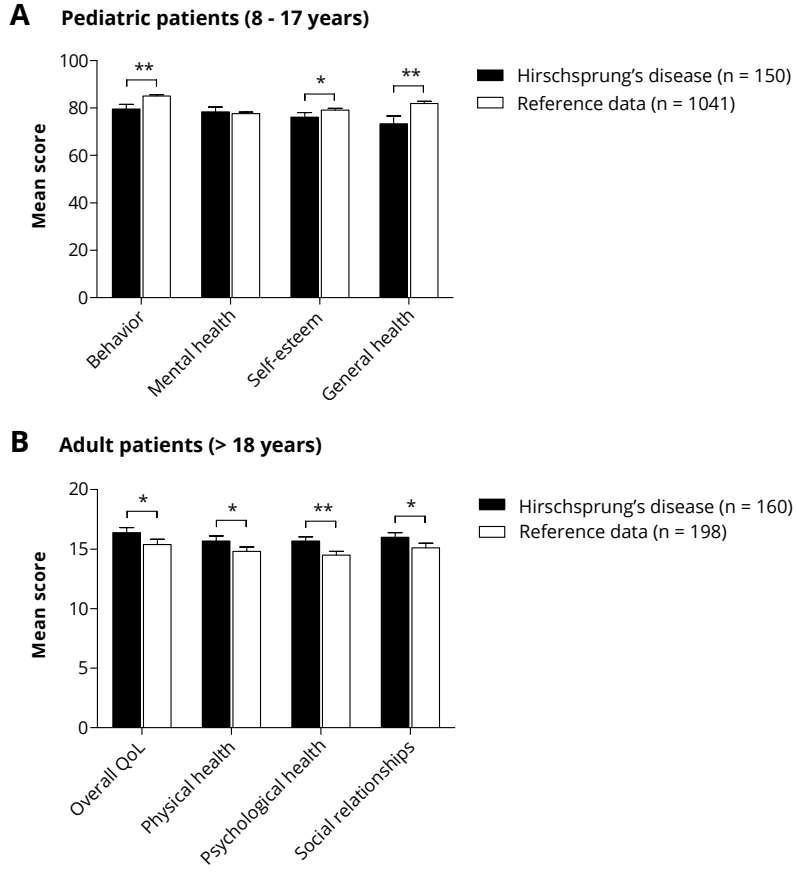

Figure 2

(A) CHQ-CF87 and (B) WHOQOL-100 domain scores of pediatric and adult patients, respectively, compared to reference data from healthy controls. Bars denote mean scores with the 95% CIs. A single asterisk denotes $P < .050$, a double asterisk denotes $P < .001$.

further contribute to impaired fecal continence. Lastly, our results showed that patients who required a redo pull-through procedure were significantly more likely to suffer from fecal incontinence. A recent study by Dingemans and colleagues indeed showed that short-term outcomes were complicated by a relatively high rate of soiling and fecal incontinence following redo pull-through procedure.[27] Important to note, however, is their finding that other functional symptoms, such as constipation and abdominal pain, improve following the redo procedure. It remains unclear to what extent the redo procedure itself contributed to the impaired fecal continence, because it may already have been worse in these patients prior to their redo procedure. We therefore merely conclude that a redo procedure may ultimately be necessary in some patients, but that one should be cautious about promising favorable functional outcomes, because the prevalence of fecal incontinence in patients after redo remains high.

In terms of QoL our results showed that pediatric HD patients had significantly lower QoL domain scores compared to the reference data. These differences may partially be explained partially by poor functional outcomes, because we found that constipation and fecal incontinence negatively influence several QoL domains. In contrast to pediatric patients, adult patients scored better on all four the domains tested compared to their respective reference data sets. This could be the result of improved functional outcomes in adult patients compared to pediatric patients. A more plausible explanation for this finding may be that adult patients develop better coping strategies to deal with their complaints. By way of illustration, adults may have more options to adapt their lives to accommodate for any defecation disorders, whereas children are often bound by fixed schedules, such as school and after-school activities.

The strength of this study was the high number of participants, thanks to all six pediatric surgery centers in the Netherlands taking part, and the relatively high response rate of 55.9%. One limitation of this study was the significant age difference in the drop-out analysis, even though the remaining variables all proved to be statistically non-significant. The difference in age between respondents and non-respondents was most likely the result of the high response rate of pediatric patients, supported by their parents, whom we found to be more motivated to participate than were adult patients. We attempted to overcome this possible inclusion bias by performing our analyses in separate age groups and by performing age and sex-matched comparisons with controls. Another limitation may be cross-sectional design of this study. A longitudinal design would have been preferable to analyze the influence of aging on functional outcomes.

Conclusions

The results of this nationwide study show that functional outcomes are better in adult

patients compared to pediatric patients, although symptoms of constipation and soiling do persist in a substantial group of adult HD patients. One factor associated with poor functional outcomes was a redo pull-through procedure, following which patients are significantly more likely to suffer from fecal incontinence. Poor functional outcomes negatively influence QoL in pediatric patients, whereas this influence diminishes partially upon reaching adulthood, indicating better coping strategies in adult patients. Persistent constipation symptoms and soiling indicate that counseling and transitional care are recommended in a specific group of patients.

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REFERENCES

1 Menezes M, Corbally M, Puri P. Long-term results of bowel function after treatment for Hirschsprung's disease: a 29-year review. Pediatr Surg Int. 2006;22:987–90.

2 Ieiri S, Nakatsuji T, Akiyoshi J, et al. Long-term outcomes and the quality of life of Hirschsprung disease in adolescents who have reached 18 years or older—a 47-year single-institute experience. J Pediatr Surg. 2010;45:2398–402.

3 Jarvi K, Laitakari EM, Koivusalo A, et al. Bowel function and gastrointestinal quality of life among adults operated for Hirschsprung disease during childhood: a population-based study. Ann Surg. 2010;252:977–81.

4 Aworanti OM, McDowell DT, Martin IM, et al. Does Functional Outcome Improve with Time Postsurgery for Hirschsprung Disease? Eur J Pediatr Surg. 2015;26:192–9.

5 Niramis R, Watanatittan S, Anuntkosol M, et al. Quality of life of patients with Hirschsprung's disease at 5 - 20 years post pull-through operations. Eur J Pediatr Surg. 2008;18:38–43.

6 Neuvonen MI, Kyrklund K, Rintala RJ, et al. Bowel Function and Quality of Life After Transanal Endorectal Pull-through for Hirschsprung Disease: Controlled Outcomes up to Adulthood. Ann Surg. 2017;265:622–9.

7 Catto-Smith AG, Trajanovska M, Taylor RG. Long-term continence after surgery for Hirschsprung's disease. J Gastroenterol Hepatol. 2007;22:2273–82.

8 Bjørnland K, Pakarinen MP, Stenstrøm P, et al. A Nordic multicenter survey of long-term bowel function after transanal endorectal pull-through in 200 patients with rectosigmoid Hirschsprung disease. J Pediatr Surg. 2017;52:1458–64.

9 Kim AC, Langer JC, Pastor AC, et al. Endorectal pull-through for Hirschsprung's disease-a multicenter, long-term comparison of results: transanal vs transabdominal approach. J Pediatr Surg. 2010;45:1213–20.

10 Rintala RJ, Pakarinen MP. Long-term outcomes of Hirschsprung's disease. Semin Pediatr Surg. 2012;21:336–43.

11 Mills JLA, Konkin DE, Milner R, et al. Long-term bowel function and quality of life in children with Hirschsprung's disease. J Pediatr Surg. 2008;43:899–905.

12 Bartlett L, Nowak M, Ho Y-H. Impact of fecal incontinence on quality of life. World J Gastroenterol. 2009;15:3276–82.

13 Belsey J, Greenfield S, Candy D, et al. Systematic review: Impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther. 2010;31:938–49.

14 Hartman EE, Oort FJ, Aronson DC, et al. Quality of life and disease-specific functioning of patients with anorectal malformations or Hirschsprung's disease: a review. Arch Dis Child. 2011;96:398–406.

15 Gosain A, Brinkman AS. Hirschsprung's Associated Enterocolitis. Curr Opin Pediatr. 2015;27:364–9.

16 Meinds RJ, Timmerman MEW, Van Meegdenburg MM, et al. Reproducibility, feasibility and validity of the Groningen Defecation and Fecal Continence Questionnaires. Scand J Gastroenterol. 2018;53:790-6.

17 Landgraf JM, Abetz L, Ware J. The CHQ user manual. Boston, MA: The Health Institute, New England Medical Center; 1996.

18 De Vries J, Van Heck GL. De Nederlandse versie van de WHOQOL-100 (The Dutch version of the WHOQOL-100). Tilburg, The Netherlands: Tilburg University; 1995.

19 Lacy BE, Mearin F, Chang L, et al. Bowel disorders. Gastroenterology. 2016;150:1393–1407e5.
20 Rao SSC, Bharucha AE, Chiarioni G, et al. Functional Anorectal disorders. Gastroenterology. 2016;150:1430–1442e4.
21 Meinds RJ, Van Meegdenburg MM, Trzpis M, et al. On the prevalence of constipation and fecal incontinence, and their co-occurence, in the Netherlands. Int J Colorectal Dis. 2017;32:475–83.
22 Timmerman MEW, Trzpis M, Broens PMA. The problem of defecation disorders in children is underestimated and easily goes unrecognized: a cross-sectional study. Eur J Pediatr [Epub ahead of print].
23 Hosli E, Detmar S, Raat H, et al. Self-report form of the Child Health Questionnaire in a Dutch adolescent population. Expert Rev Pharmacoecon Outcomes Res. 2007;7:393–401.
24 The WHOQOL Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med. 1998;46:1569–85.
25 Heikkinen M, Rintala R, Luukkonen P. Long-term anal sphincter performance after surgery for Hirschsprung's disease. J Pediatr Surg. 1997;32:1443–6.
26 Meinds RJ, Eggink MC, Heineman E, et al. Dyssynergic defecation may play an important role in postoperative Hirschsprung's disease patients with severe persistent constipation: Analysis of a case series. J Pediatr Surg. 2014;49:1488–92.
27 Dingemans AJM, van der Steeg HJJ, Rassouli-Kirchmeier R, et al. Redo pull-through surgery in Hirschsprung's disease: Short-term clinical outcome. J Pediatr Surg. 2017;52:1446–50.

CHAPTER 9

Matched comparison of outcomes following Duhamel and transanal endorectal pull-through procedures in patients with Hirschsprung's disease

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In preparation

SUMMARY

Background

The majority of Dutch Hirschsprung's disease (HD) patients are operated by either Duhamel or transanal endorectal pull-through (TERPT) procedure. The aim of this study was to perform a sex- and age-matched comparison of the long-term functional outcomes of both procedures.

Methods

From a nationwide cross-sectional study, we selected 52 patients who had underwent a TERPT procedure (mean age 12±2 years) and performed an age- and gender-matched comparison to peers who had underwent a Duhamel procedure and to healthy controls. Functional outcomes were assessed by the Constipation Scoring System (CSS), Continence Grading Scale (CGS). We additionally assessed if surgical approach, *i.e.* laparotomy, laparoscopy or transanal, influenced outcomes.

Results

The median CSS was comparable following Duhamel and TERPT procedures (5 versus 4), but significantly higher compared to controls ($P < .001$). Laxative usage was more frequent following Duhamel procedure compared to TERPT procedure (48% versus 12%, $P < .001$). The CGS was comparable following either procedure (4 versus 5), but significantly greater than in controls ($P = .003$ and $P < .001$). Compared to open Duhamel procedures, laparoscopic procedures resulted in significant lower laxative usage ($P = .017$) and soiling ($P = .007$). TERPT procedures that were performed transanal resulted in higher prevalences of urge incontinence for feces ($P < .001$) and urine ($P = .006$), compared to laparoscopic procedures.

Conclusions

The differences in functional outcomes following Duhamel and TERPT procedures are limited. Duhamel procedure outcomes can be further improved by opting for laparoscopy instead of an open approach, whereas TERPT outcomes can be improved when performed laparoscopically, instead of completely transanal.

INTRODUCTION

Hirschsprung's disease (HD) is a congenital condition of the distal intestines characterized by absence of ganglion cells and intractable constipation. Because of the severity of constipation, the vast majority of HD patients require a surgical procedure to resect the affected intestines.

In the majority of Dutch HD patients, the resection of affected intestines is done by either Duhamel or transanal endorectal pull-through (TERPT) procedure.[1,2] The Duhamel procedure constructs a new rectal pouch by a posterior side-to-side anastomosis of aganglionic rectum and ganglionic intestines,[1] whereas the TERPT procedure consists of a transanal pull-through of ganglionic intestines followed by a very low direct anastomosis just above the dentate line.[2] The latter can be done using a short aganglionic muscular cuff by a transanal submucosal dissection (*i.e.* Soave-like)[2,3] or by a full-thickness dissection of the bowel wall (*i.e.* Swenson-like).[4]

Both Duhamel and TERPT procedures have been compared before, albeit with small heterogeneous groups and inconclusive results.[5–9] The general consensus, however, is that both procedures have their advantages and downsides.[10] Firstly, the retrorectal approach of the Duhamel procedure is thought to avoid the nerves located anterior of the rectum, thus limiting iatrogenic nerve damage. In turn, there may be increased constipation complaints because of the residual aganglionic rectum. Secondly, the TERPT procedure can be performed completely transanal, thus reducing the chance of post-operative adhesions by avoiding extensive manipulation in the peritoneal cavity and resulting in better cosmetic results since less scar tissue will be seen on the abdominal wall.[3,9] However, there have been concerns that this approach may have an increased risk of anal sphincter damage by overt stretching during the procedure.[11,12]

Because of the heterogeneity of previous studies,[5–9] we decided to perform a gender- and age-matched analysis on the long-term outcomes of both techniques. Given the nature of both procedures, we hypothesize that there may be an increased severity of fecal incontinence following the TERPT procedure because of overstretching of the anal sphincter, whereas the Duhamel procedure may be followed by an increased tendency towards constipation because of the residual aganglionic rectum. The aim of this study was to perform a matched comparison of the long-term functional outcomes of both procedures, concerning constipation, fecal continence, and urinary continence.

METHODS

Study design

We recently performed a nationwide cross-sectional study of the long-term outcomes in HD in collaboration with six pediatric surgery centers.[13] For this study, we analyzed the medical records of all known HD patients born between 1955 and 2009, which resulted in a data base consisting of 830 HD patients. Following the exclusion of ineligible patients (for example passed away, permanent stoma, intellectual disability, no known address), we invited 619 patients and their parents or caregivers to participate and complete questionnaires on anorectal functioning and quality of life. Following this invitation, a total of 389 (55.2%) responded and completed questionnaires. For our current study, we included 52 pediatric respondents who had undergone a TERPT procedure. These were matched on sex and age to 52 pediatric respondents who had underwent a Duhamel procedure.

These two groups were compared on variables such as age at time of surgery, surgical approach (laparotomy, laparoscopy, or transanal), surgical complications, post-operative enterocolitis, and additional treatments (for example, sphincterectomy, dilatation, botulinium injection, or redo pull-through). Surgical complications were defined as complications that occurred within 30 days of and that were the direct result of the initial surgical intervention (for example, anastomotic leakage, wound infection, adhesions). Post-operative enterocolitis was defined as the presence of symptoms such as abdominal distention, diarrhea, bloody stools, and/or fever with the intention-to-treat as such.[14]

Next, we additionally matched 52 healthy controls on age and gender that we randomly selected from a previous study we conducted in the Dutch general population,[15] thus resulting in three comparable groups. Using the questionnaire data, we then assessed functional outcomes and urinary continence in the three groups.

Differences in surgical procedures and follow-up

There was a variation in surgical procedures performed in the six participating surgical centers. The Duhamel procedure was performed in center A (n = 33), center B (n = 9), and center C (n = 10). The TERPT procedure was performed with a transanal submucosal dissection (*i.e.* Soave-like) in center D (n = 11), center E (n = 7), center B (n = 5), and center C (n = 2), whereas it was performed with a full-thickness dissection (*i.e.* Swenson-like) in center F (n = 27). In each surgical center, a maximum of three pediatric surgeons is responsible for carrying out or supervising the surgical treatment of HD.

Aside from surgical preferences, the remainder of the treatment and follow-up of HD patients in the Netherlands have been standardized following a collaboration between

all six pediatric surgical centers and the national patient association.[16] This healthcare standard guarantees a comparable and sufficient follow-up for all HD patients in the Netherlands.

Assessment of functional outcomes

The functional outcomes were assessed using patients' answers on the anorectal functioning questionnaire (P-DeFeC questionnaire).[17]

The severity of constipation was assessed by the Constipation Scoring System (CSS) by Agachan and colleagues.[18] The CSS consists of 8 items totaling a score between 0 and 30 points, for which 0 is no constipation and 30 is extreme constipation. Items include defecation frequency, painful evacuation, incomplete defecation, abdominal pain, time on lavatory, need for assistance, failure to evacuate, and duration of constipation. Using the questionnaire, we additionally scored the use of laxatives, rectal suppositories, and the need for rectal irrigation as therapy for constipation, all had to be used at least several times per month.

The severity of fecal incontinence was assessed by the Continence Grading Scale (CGS) by Jorge and colleagues,[19] where a score of 0 implies perfect continence and 20 complete incontinence. The CGS consists of 5 items, including incontinence for solid stool, incontinence for liquid stool, incontinence for gas, need to wear pads, and lifestyle alterations. We additionally looked at several subtypes of fecal incontinence, of which all had to occur at least multiple times per month. Soiling was defined as the loss of small amounts of feces or staining of underwear, urge incontinence as being unable to reach the toilet in time after feeling of urge, incontinence for liquid stool as loss of watery stools or diarrhea, and incontinence for solid stool as loss of large amounts of solid feces without having felt urge. Using the questionnaire, we additionally scored the need for rectal irrigation as therapy for fecal incontinence.

Lastly, we assessed anorectal sensations, that is the ability to feel urge and the ability to differentiate types of stool.

Assessment of urinary continence

In the DeFeC questionnaire a section on urinary incontinence was included. Based on the answers given by patients, we defined stress incontinence as involuntary urine loss upon effort, coughing, sneezing, or exertion. Urge incontinence was defined as the involuntary loss of urine prior to reaching the toilet. Nightly incontinence was defined as the involuntary loss of urine while asleep. Post-micturition dribble was defined as the loss of urine while getting dressed after urinating. Lastly, involuntary loss for no clear reason or continuously was defined as such.

Statistical analysis

Data were analyzed using SPSS 23.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY). Proportions were reported as prevalence percentages. Continuous variables were reported as median with minimum and maximum or as mean with standard deviation (SD), depending on the normality of distribution. The statistical tests that were used were limited to Pearson's chi-square test, Mann-Whitney U-test, and Students' t test which were used appropriately. Two-sided *P* values of less than .050 were considered statistically significant.

Table 1 Patient and clinical characteristics

	Duhamel No. (%)	TERPT No. (%)	*P* value
Overall	52 (100)	52 (100)	
Patient characteristics			
Male sex	46 (88)	46 (88)	1.000
Age at follow-up (years)[a]	13 ± 2	12 ± 2	.195
Length of aganglionosis			.315
Rectosigmoid	45 (87)	46 (88)	
Long segment	3 (6)	5 (10)	
Total colonic	4 (8)	1 (2)	
Congenital comorbidities	5 (10)	6 (12)	.750
Clinical characteristics			
Age at time of surgery (days)[b]	135 (8 – 1867)	148 (15 – 1333)	.782
Surgical approach			< .001
Laparotomy	41 (79)	1 (2)	
Laparoscopy	11 (21)	40 (77)	
Transanal	0 (0)	11 (21)	
Surgical complication	7 (13)	2 (4)	.081
Post-operative enterocolitis	12 (23)	8 (15)	.320
Additional treatments			
Anal sphincterectomy	1 (2)	0 (0)	.315
Anal dilatation	2 (4)	8 (15)	.046
Anal botulinium injection	6 (12)	6 (12)	1.000
Redo pull-through	4 (8)	6 (12)	.506

[a] Mean ± SD

[b] Median (minimum – maximum)

RESULTS

Patient and clinical characteristics

A total of 104 patients who had undergone Duhamel (n = 52) or TERPT procedure (n = 52) were included. Patient characteristics are listed in Table 1. Following matching, there were no significant differences in the distribution of sex, mean age, length of aganglionosis, and comorbidities between the two groups (Table 1). The majority (79%) of the Duhamel procedures were performed using laparotomy, while TERPT was primarily performed laparoscopy-assisted (77%, $P < .001$) (Table 1). Moreover, patients treated by TERPT procedure more often underwent anal dilation compared to patients treated by Duhamel procedure (15% versus 4%, $P = .046$, Table 1).

Comparison of functional outcomes

The severity of constipation, assessed by the CSS, was comparable in patients treated by either procedure, whereas it was significantly higher in both groups of patients compared to healthy controls ($P < .001$, Table 2). With regards to therapy usage for constipation, nearly half (48%) of the Duhamel group reported using laxatives at least several times per month, compared to only 12% in the TERPT group ($P < .001$, Table 2). The usage of rectal suppositories was comparable in both groups of patients and controls (Table 2). Rectal irrigation for constipation was comparable in both groups of patients (11% versus 11%), but significantly higher when compared to controls (0%, $P < .001$, Table 2).

There was no difference in the severity of fecal incontinence, assessed by the CGS, between patients treated by either procedure. However, the severity of fecal incontinence was significantly greater in patients treated by either Duhamel (median score 4) or TERPT procedure (median score 5) compared to controls (median score 2, $P = .003$ and $P < .001$, respectively, Table 2). Soiling was the most common type of fecal incontinence in both groups of patients, with a prevalence of 35% following Duhamel procedure and 42% following TERPT procedure. There were no differences in the prevalence of subtypes of fecal incontinence between patients treated by either procedure (Table 2). Rectal irrigation for the treatment of fecal incontinence was comparable in the Duhamel and TERPT group (12% versus 13%), and significantly higher compared to controls (0%, $P = .036$ and $P = .019$, respectively, Table 2).

Next, we compared anorectal sensation, i.e. the ability to feel urge and ability to differentiate types of stool (Figure 1). There was no difference in the ability to feel urge between patients treated by Duhamel or TERPT procedure. Controls, however, significantly more often felt urge compared to patients treated by Duhamel ($P = .001$) and TERPT procedure ($P = .003$) (Figure 1A). The ability to differentiate types of stool (Figure

1B) were not significantly different between the three groups.

Comparison of urinary continence

There were no differences in the prevalences of any subtype of urinary incontinence between the groups of patients treated by Duhamel and TERPT procedure (Table 2). However, compared to healthy controls, patients who had underwent a Duhamel procedure suffered significantly more often from continuous urinary incontinence (10% versus 0%, P = .022, Table 2). Following TERPT procedure, patients suffered significantly more often from nightly urinary incontinence (13%, P = .027) and continuous urinary incontinence (8%, P = .041) compared to healthy controls (Table 2).

Comparison of Duhamel approaches

We additionally compared the outcomes of Duhamel procedures that were performed using laparotomy (*i.e.* open Duhamel, n = 41) and the Duhamel procedures that were performed using laparoscopy (*i.e.* laparoscopic Duhamel, n = 11) (Table 3). Importantly, there were no differences in distribution of sex, age, or length of aganglionosis between the two Duhamel approaches (Table 3). The severity of constipation, as indicated by the CSS score, and the severity of fecal incontinence, as indicated by the CGS score,

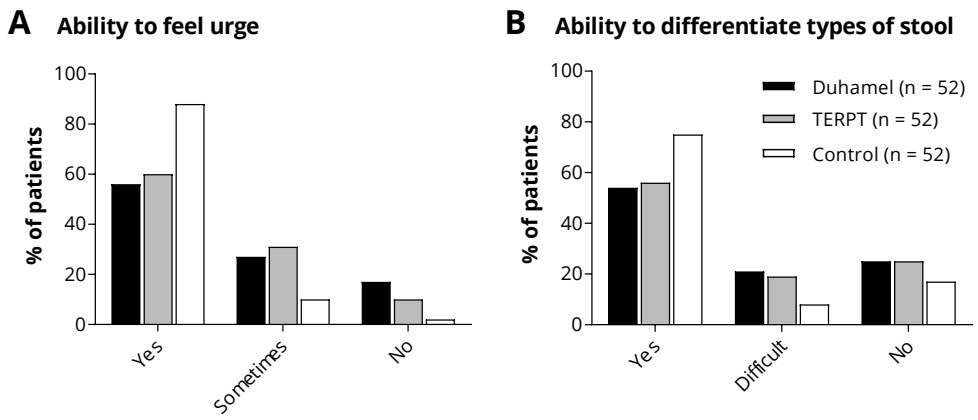

Figure 1

Comparison of anorectal sensation.

A: There was no difference in the feeling of urge between patients treated by Duhamel or TERPT procedure. Controls significantly more often felt urge compared to patients treated by Duhamel (P = .001) and TERPT procedure (P = .003).

B: The ability to differentiate types of stool was comparable between the three groups (no significant differences).

Table 2
Comparison of functional outcomes

	Duhamel (n = 52), No. (%)	TERPT (n = 52), No. (%)	Controls (n = 52), No. (%)	*P* values		
	A	B	C	A vs B	A vs C	B vs C
Constipation						
CSS (median, range)	5 (1 – 20)	4 (0 – 15)	2 (0 – 9)	.293	< .001	< .001
Laxative usage	25 (48)	6 (12)	1 (2)	< .001	< .001	.050
Rectal suppository usage	2 (4)	2 (4)	0 (0)	1.000	.153	.153
Rectal irrigation for constipation	11 (21)	11 (21)	0 (0)	1.000	< .001	< .001
Fecal continence						
CGS (median, range)	4 (0 – 15)	5 (0 – 12)	2 (0 – 8)	.359	.003	< .001
Soiling	18 (35)	22 (42)	4 (8)	.420	.001	< .001
Urge incontinence	4 (8)	4 (8)	1 (2)	1.000	.169	.169
Incontinence for solid stool	6 (12)	3 (6)	1 (2)	.295	.050	.308
Incontinence for liquid stool	7 (13)	3 (6)	0 (0)	.183	.006	.079
Rectal irrigation for incontinence	6 (12)	7 (13)	0 (0)	.767	.036	.019
Urinary continence						
Stress incontinence	2 (4)	1 (2)	4 (8)	.558	.400	.169
Urge incontinence	2 (4)	2 (4)	0 (0)	1.000	.153	.153
Nightly incontinence	6 (12)	7 (13)	1 (2)	.767	.050	.027
Post-micturition dribble	1 (2)	0 (0)	2 (4)	.315	.558	.153
Continuous or no clear cause	5 (10)	4 (8)	0 (0)	.727	.022	.041

TERPT = Transanal endorectal pull-through, CSS = Constipation Scoring System, CGS = Continence Grading Scale

was comparable following both approaches (Table 3). Compared to open Duhamel procedures, patients treated laparoscopically had a significantly lower usage of laxatives (59% versus 18%, *P* = .017), and had a lower prevalence of soiling (44% versus 0%, *P* = .007) (Table 3). The rest of the tested variables were comparable in the two approaches (Table 3).

Table 3
Comparison of Duhamel approaches

	Open Duhamel (n = 41), No. (%)	Laparoscopic Duhamel (n = 11), No. (%)	*P* value
Patient characteristics			
Male sex	37 (90)	9 (82)	.437
Age (median, range)	13 (9 – 19)	13 (9 – 16)	.821
Rectosigmoid variant	37 (90)	8 (73)	.277
Constipation			
CSS (median, range)	5 (1 – 19)	5 (1 – 20)	.398
Laxative usage	24 (59)	2 (18)	.017
Rectal suppository usage	2 (5)	0 (0)	.455
Rectal irrigation for constipation	9 (22)	2 (18)	.786
Fecal continence			
CGS (median, range)	4 (1 – 15)	2 (0 – 15)	.175
Soiling	18 (44)	0 (0)	.007
Urge incontinence	4 (10)	0 (0)	.281
Solid stool incontinence	6 (15)	0 (0)	.177
Liquid stool incontinence	7 (17)	0 (0)	.141
Rectal irrigation for incontinence	5 (12)	1 (9)	.775
Urinary continence			
Stress incontinence	2 (5)	0 (0)	.455
Urge incontinence	2 (5)	0 (0)	.445
Nightly incontinence	5 (12)	1 (9)	.775
Post-micturition dribble	1 (2)	0 (0)	.601
Continuous or no clear cause	4 (10)	1 (9)	.947

CSS = Constipation Scoring System, CGS = Continence Grading Scale

Comparison of TERPT approaches

Next, we compared the outcomes of TERPT procedures that were performed using laparoscopy (*i.e.* laparoscopic TERPT, n = 40) with the TERPT procedures that were performed completely transanal (*i.e.* transanal TERPT, n = 11) (Table 4). There were no significant differences in sex, age, and length of aganglionosis between the two TERPT approaches (Table 4). There were no significant differences in the severity of constipation

Table 4
Comparison of TERPT approaches

	Laparoscopic TERPT (n = 40), No. (%)	Transanal TERPT (n = 11), No. (%)	*P* value
Patient characteristics			
Male sex	35 (88)	10 (91)	.756
Age (median, range)	13 (8 – 17)	12 (10 – 14)	.342
Rectosigmoid variant	35 (88)	11 (100)	.467
Constipation			
CSS (median, range)	4 (0 – 15)	3 (0 – 10)	.954
Laxative usage	4 (10)	2 (18)	.456
Rectal suppository usage	2 (5)	0 (0)	.449
Rectal irrigation for constipation	8 (20)	3 (27)	.603
Fecal continence			
CGS (median, range)	4 (0 – 12)	6 (2 – 11)	.076
Soiling	15 (38)	6 (55)	.309
Urge incontinence	0 (0)	4 (36)	< .001
Solid stool incontinence	1 (3)	2 (18)	.050
Liquid stool incontinence	1 (3)	2 (18)	.050
Rectal irrigation for incontinence	4 (15)	3 (30)	.295
Urinary continence			
Stress incontinence	0 (0)	1 (9)	.054
Urge incontinence	0 (0)	2 (18)	.006
Nightly incontinence	4 (10)	2 (18)	.456
Post-micturition dribble	0 (0)	0 (0)	
Continuous or no clear cause	2 (5)	2 (18)	.150

TERPT = Transanal endorectal pull-through, CSS = Constipation Scoring System, CGS = Continence Grading Scale

and fecal incontinence, as indicated by CSS and CGS score, respectively, following both TERPT approaches (Table 4). However, patients treated by a completely transanal TERPT procedure had significantly higher prevalences of urge incontinence for feces (36% versus 0%, $P < .001$) and urine (18% versus 0%, $P = .006$), compared to patients treated by laparoscopic TERPT. The rest of the tested variables were not significantly different between the two approaches (Table 4).

DISCUSSION

In contrast to what we hypothesized, there were no significant differences in the severity of constipation and fecal incontinence following Duhamel and TERPT procedures. The higher usage of laxatives in the total group of Duhamel procedures may be an indication of a greater tendency towards constipation in this group. Nevertheless, we showed that this may be negated by performing a laparoscopic Duhamel procedure, following which the usage of laxatives was significantly lower. Last, our results showed that patients who underwent a completely transanal TERPT procedure had significant higher prevalences of urge incontinence for both feces and urine compared to patients who underwent a laparoscopic TERPT procedure.

With regards to long-term functional outcomes, there is currently little evidence that substantiates the decision to prefer either technique over the other. Multiple studies have compared the outcomes of Duhamel and TERPT procedures, often with varying results, and often based on small heterogeneous patient groups.[5–8] A major flaw in these studies is the difference in age between the two compared groups, resulting from the use of patients from different time cohorts, and subsequently biasing results. A recent meta-analysis by Chen and colleagues therefore concluded that the current quality of evidence is too low to draw any conclusions on the comparison of functional outcomes following both techniques.[9] We therefore performed a sex- and age-matched comparison of patients operated with both techniques, limiting bias by these factors, which showed that the differences between both techniques, if any, are small. The only notable difference between both techniques was the higher usage of laxatives following the Duhamel procedure. First, this difference may result from differences between healthcare providers and surgical centers, whereby some may be faster inclined to prescribe laxatives than others. Second, the difference in laxative usage may result from structural differences in both surgical techniques. This line of reasoning is supported by the postulation that the pouch created in the Duhamel procedure, partially consisting of native aganglionic rectum, may continue to impair bowel function, thus leading to an increased tendency to constipation.[20] In any case, this difference between Duhamel and

TERPT procedure may be negated by performing a laparoscopic Duhamel procedure, following which the usage of laxatives was significantly lower.

Contrary to what we hypothesized, there was no significant difference in the prevalence of fecal incontinence, nor in the prevalence of urinary incontinence, following Duhamel or TERPT procedure. It therefore seems that the potential iatrogenic nerve damage is not necessarily greater following TERPT procedure. Importantly, we found that both fecal and urinary continence may be further improved by avoiding the completely transanal approach during TERPT procedure, and instead opting for assisting the TERPT with laparoscopy. This contradicts a previous meta-analysis by Thomson and colleagues[21] which found no differences between the two approaches. It must be noted however, that all the included studies were retrospective case studies and that the authors of the meta-analysis themselves concluded that the overall quality of studies was low. There may be several reasons for the difference in continence following both TERPT approaches. First, the completely transanal TERPT approach may be troubled by a limited, or even absent, view of the pelvic anatomic structures. The reduced view may increase the risk of iatrogenic pelvic nerve damage, thus resulting in a higher risk of impaired continence. Second, impaired continence may result from a prolonged stress on the anal sphincter during the completely transanal approach. Based on these results, it is unfortunately not possible to differentiate between the two aforementioned reasons. Possible future studies should therefore include extensive anorectal manometric investigations, allowing the comparison of anal sphincter functioning between patients treated by either TERPT approach. A last argument for performing the TERPT procedure in combination with laparoscopy is that it allows for a more precise assessment of the transitional zone, as this has been proven to be difficult to predict pre-operatively.[22]

Certain limitations, as well as strengths, should be taken into account before drawing conclusions. First, because multiple surgical centers participated, there may have been a variation in post-operative treatment and follow-up. We believe these differences were limited, as the care of HD has been nationally standardized following a collaboration between the six surgical centers and the national patient association,[16] guaranteeing a minimal level of care for all HD patients. Second, another limitation of this study may be the difference in TERPT procedures, of which nearly half was performed Soave-like, while the rest was performed Swenson-like. We have decided to group these patients together as a previous report has shown that the two techniques are comparable.[23] This reasoning was confirmed by the outcomes of our own subanalyses, which showed no significant differences in any of the tested variables between Swenson-like and Soave-like TERPT procedures, after the exclusion of the completely transanal TERPT procedures (data not shown). Meanwhile, a strength of this study was the number of investigated variables,

including clinical aspects such as complications and episodes of enterocolitis, as well as long-term functional outcomes, including urinary continence. Lastly, the major strength of this study over previous studies on the same subject is that we performed a gender- and age-matched analysis. This has resulted in two comparable groups of patients, of the same age, and with comparable lengths of follow-up, wherein the only difference was the type of surgical procedure.

Conclusions

In conclusion, the differences in functional outcomes following Duhamel and TERPT procedures, if any, are small. Importantly, the outcomes of the Duhamel procedure can be further improved by opting for laparoscopy instead of an open approach, whereas the outcomes of the TERPT procedure can be improved by assisting the procedure with laparoscopy, instead of performing it completely transanal.

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REFERENCES

1 Duhamel B. A new operation for the treatment of Hirschsprung's disease. Arch Dis Child. 1960;35:38–9.

2 la Torre-Mondragón L De, Ortega-Salgado JA. Transanal endorectal pull-through for Hirschsprung's disease. J Pediatr Surg. 1998;33:1283–6.

3 la Torre L De, Ortega A. Transanal versus open endorectal pull-through for Hirschsprung's disease. J Pediatr Surg. 2000;35:1630–2.

4 Langer JC. Laparoscopic and transanal pull-through for Hirschsprung disease. Semin Pediatr Surg. 2012;21:283–90.

5 Martins ECS, Peterlini FL, Fagundes DJ, et al. Clinical, manometric and profilometric evaluation after surgery for Hirschsprung's disease: comparison between the modified Duhamel and the transanal rectosigmoidectomy techniques. Acta Cir Bras. 2009;24:416–22.

6 Tannuri ACA, Tannuri U, Romão RLP. Transanal endorectal pull-through in children with Hirschsprung's disease—technical refinements and comparison of results with the Duhamel procedure. J Pediatr Surg. 2009;44:767–72.

7 Gunnarsdóttir A, Larsson LT, Arnbjörnsson E. Transanal Endorectal vs. Duhamel Pull-Through for Hirschsprung's Disease. Eur J Pediatr Surg. 2010;20:242–6.

8 Giuliani S, Betalli P, Narciso A, et al. Outcome Comparison Among Laparoscopic Duhamel, Laparotomic Duhamel, and Transanal Endorectal Pull-Through: A Single-Center, 18-Year Experience. J Laparoendosc Adv Surg Tech. 2011;21:859–63.

9 Chen Y, Nah SA, Laksmi NK, et al. Transanal endorectal pull-through versus transabdominal approach for Hirschsprung's disease: A systematic review and meta-analysis. J Pediatr Surg. 2013;48:642–51.

10 Arts E, Botden SMBI, Lacher M, et al. Duhamel versus transanal endorectal pull through (TERPT) for the surgical treatment of Hirschsprung's disease. Tech Coloproctol. 2016;20:677–82.

11 El-Sawaf MI, Drongowski RA, Chamberlain JN, et al. Are the long-term results of the transanal pull-through equal to those of the transabdominal pull-through? A comparison of the 2 approaches for Hirschsprung disease. J Pediatr Surg. 2007;42:41–7.

12 Stensrud KJ, Emblem R, Bjornland K. Anal endosonography and bowel function in patients undergoing different types of endorectal pull-through procedures for Hirschsprung disease. J Pediatr Surg. 2015;50:1341–6.

13 Meinds RJ, van der Steeg AFW, Sloots CEJ, et al. Long-term functional outcomes and quality of life in patients with Hirschsprung's disease. Br J Surgery (In press).

14 Gosain A, Brinkman AS. Hirschsprung's Associated Enterocolitis. Curr Opin Pediatr. 2015;27:364–9.

15 Timmerman MEW, Trzpis M, Broens PMA. The problem of defecation disorders in children is underestimated and easily goes unrecognized: a cross-sectional study. Eur J Pediatr [Epub ahead of print].

16 Patient Association Hirschsprung's Disease (2013). Healthcare standard Hirschsprung's disease. http://www.zorgstandaarden.net/zza/media/zorgstandaard/20140211-001/files/assets/basic-html/index.html#1. Accessed 5 May 2018.

17 Meinds RJ, Timmerman MEW, Van Meegdenburg MM, et al. Reproducibility, feasibility and validity of the Groningen Defecation and Fecal Continence Questionnaires. Scand J

Gastroenterol. 2018;53:790–6.
18 Agachan F, Chen T, Pfeifer J, et al. A constipation scoring system to simplify evaluation and management of constipated patients. Dis Colon Rectum. 1996;39:681–5.
19 Jorge JM, Wexner SD. Etiology and management of fecal incontinence. Dis Colon Rectum. 1993;36:77–97.
20 Lawal TA, Chatoorgoon K, Collins MH, et al. Redo pull-through in Hirschprung's disease for obstructive symptoms due to residual aganglionosis and transition zone bowel. J Pediatr Surg. 2011;46:342–7.
21 Thomson D, Allin B, Long AM, et al. Laparoscopic assistance for primary transanal pull-through in Hirschsprung's disease: a systematic review and meta-analysis. BMJ Open. 2015;5:e006063.
22 Muller CO, Mignot C, Belarbi N, et al. Does the radiographic transition zone correlate with the level of aganglionosis on the specimen in Hirschsprung's disease? Pediatr Surg Int. 2012;28:597–601.
23 Nasr A, Haricharan RN, Gamarnik J, et al. Transanal pullthrough for Hirschsprung disease: Matched case–control comparison of Soave and Swenson techniques. J Pediatr Surg. 2014;49:774–6.

CHAPTER 10

Dyssynergic defecation may play an important role in postoperative Hirschsprung's disease patients with severe persistent constipation

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SUMMARY

Background

After surgery for Hirschsprung's disease (HD) the majority of patients have satisfactory clinical outcomes. Nevertheless, a substantial number of patients remain who suffer from severe persistent constipation. Current consensus attributes these complaints to the hallmarks of HD. In non-HD patients a cause for severe constipation is dyssynergic defecation.

Methods

Retrospectively, we reviewed the medical records of ten post-operative HD patients with severe persistent constipation who had undergone extensive anorectal function tests to diagnose the reason for the constipation. We analyzed the results of these tests.

Results

During the last three years, ten post-operative HD patients with severe persistent constipation were given extensive anorectal function tests. All ten patients were diagnosed with dyssynergic defecation. The ages at the time of diagnosis ranged from 7 to 19 years with a median age of 12 years. Signs of an enlarged rectum were seen in all ten patients, with a maximum measured value of 845 mL.

Conclusions

Patients with HD may also suffer from dyssynergic defecation. It is important to consider this possibility when dealing with severe persistent constipation in post-operative HD patients. Viable options for treating dyssynergic defecation are available that could prevent irreversible long-term complications.

INTRODUCTION

Hirschsprung's disease (HD) is a birth defect characterized by aganglionosis of the distal colon. Due to obstipation proximal to the affected segment of the colon HD often presents with a failure to pass meconium during the first 24 to 48 hours after birth. Incidence numbers are estimated to be 1 in 5000 live births, with a pronounced predominance of males over females.[1,2]

Nowadays, after surgery for HD, the majority of patients have satisfactory clinical outcomes with mild constipation, especially after reaching adulthood.[3–5] Some reports, however, show a substantial number of patients with complaints including severe persistent constipation and fecal soiling.[6–9] Constipation in post-operative HD patients may be caused by the absence of the internal anal sphincter reflex or by a residual part of aganglionic colon remaining after surgical reconstruction. Neither of these causes, however, explains why some patients suffer from severe constipation while others have no defecation problems whatsoever.

Apart from the two causes mentioned there are other causes with good treatment options that could be responsible for the severe constipation seen in some HD patients. One is dyssynergic defecation, a disorder characterized by a paradoxical involuntary contraction of the external anal sphincter which leads to a functional neuromuscular obstruction (Figure 1).[10] Recently, another study showed that dyssynergic defecation is responsible for severe constipation in patients with inflammatory bowel disease.[11] While

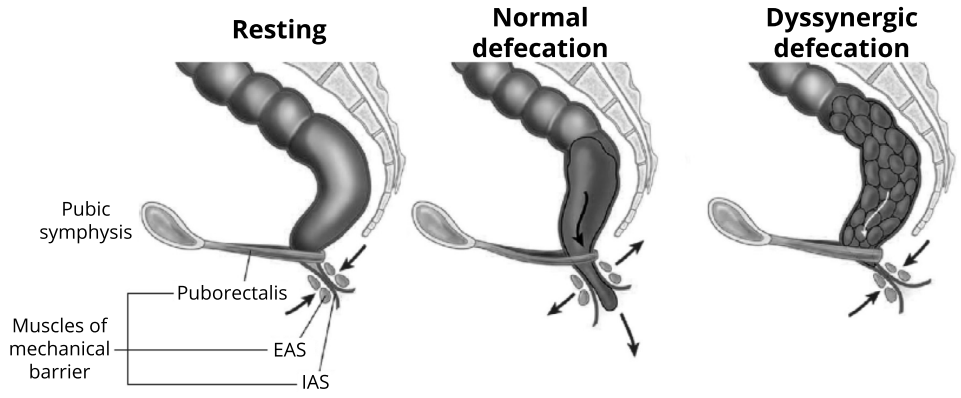

Figure 1
A schematic representation of the normal defecation process and of dyssynergic defecation. During squeeze the external anal sphincter and the puborectal muscle are contracted and they create a mechanical barrier for stool. In normal defecation the puborectal muscle and the external anal sphincter relax, so that stool can be evacuated. In pelvic floor dyssynergia there is a paradoxical involuntary contraction of the external anal sphincter and the puborectal muscle.

the exact cause of dyssynergic defecation is unknown for the majority of the affected patients, development during childhood, pregnancy, and trauma have been identified as possible causes that might set off the defecation problems.[12] Most constipation complaints in HD patients are attributed to the disease itself. Nevertheless, it is possible that some HD patients have never mastered the act of defecation properly due to pre-operative obstipation and post-operative pain in the anal canal causing them to suffer from dyssynergic defecation as a result.[13] Thus besides being unable to relax their internal anal sphincter, HD patients might have the additional problem that their external anal sphincter contracts involuntary during defecation.

With all this in mind, we gave HD patients with severe persistent constipation a full anorectal examination, which consisted of an anal pressure profile, balloon retention test, and defecometry. We hypothesized that not all post-operative defecation complaints were attributable to HD and that dyssynergic defecation – for which viable treatment options are available – may increase the severity of constipation in these patients.

METHODS

Patient selection

Between May 2010 and May 2013, HD patients who presented with severe persistent constipation were given extensive anorectal function tests in order to diagnose the cause of their constipation. Inclusion criteria for undergoing anorectal function tests were histopathologically proven HD, proper treatment for HD, capable of understanding the tasks involved in the anorectal function tests, and severe persistent constipation that met the criteria of Rome III for functional constipation. Exclusion criteria were other evident causes of constipation in HD such as stenosis of the anastomosis or residual aganglionosis. A positive test result for dyssynergic defecation either meant inappropriate contraction of the pelvic floor or less than 20% relaxation of basal resting sphincter pressure with sufficient propulsive force during attempted defecation, as described in the Rome III criteria. Upon diagnosis, we referred patients to a specialized pelvic floor physiotherapist. We collected and reviewed the medical records and test results of these patients retrospectively.

In addition, we reviewed the patients' clinical records to collect variables such as the variant of HD, duration of constipation, applied treatment, relevant co-morbidities, episodes of Hirschsprung's associated enterocolitis, and post-operative complications.

Measuring equipment

We recorded and analyzed the data with solar gastrointestinal high resolution manometry

equipment (Medical Measurement Systems, Enschede, the Netherlands), version 8.23.

Catheter 1: We used Unisensor K12981 solid-state (Boston type) circumferential catheters with an outer diameter of 12F with which we could measure circumferential pressure every 8 mm over a total length of 6.8 cm into the rectum.

Catheter 2: We used Unisensor K14204 catheters with an outer diameter of 14F with two microtip sensors to connect the rectal balloon, to inflate it, and to register the pressure inside the balloon. The solar gastrointestinal high resolution manometry equipment corrected the pressure in the rectal balloon for the resistance of the balloon itself, so that only the true pressure of the rectum was reported.

Tests

The anal pressure profile

For this test we carefully fixed Catheter 1 to the patient's buttocks near the anal canal with adhesive tape to prevent slippage during the procedure. We obtained basal anal pressure measurements while the subject was at rest while we recorded the maximum voluntary sphincter pressure during sustained and maximum pelvic floor contractions three times. We used the highest of the three values for our analysis.

Balloon retention test

For this test we also carefully fixed Catheter 1 to the patient's buttocks near the anal canal with adhesive tape to prevent slippage during the procedure. Next to Catheter 1 we connected a collapsed, non-latex balloon to Catheter 2 and placed it in the rectum. While installing the catheters the patient was in the left lateral recumbent position but we administered this test with the patient sitting upright on a commode. When the patient was completely at rest we very slowly filled the balloon with water of 37°C (0.5 mL/second for children younger than 12 years or 1.0 mL/second for older children and adults). Meanwhile, we recorded the pressure in the rectal balloon and the volume inflated.

We asked the patients to retain the balloon as long as possible and to report when they experienced the first sensation (some rectal feeling), constant sensation (at home, the patient would go to the toilet), urge sensation (the patient would first go to the toilet before continuing any other activity), and the maximum tolerable sensation level. We stopped testing when the patient reached maximum tolerable sensation, *i.e.* when filling reached the limit of tolerance or maximum retainable volume if the patient had lost the balloon earlier. Then we emptied the balloon completely. This technique has been described previously.[14–16] It provides information about the extent to which the patient experiences rectal filling, rectal capacity, rectal compliance, and whether the anal canal responds to rectal filling by squeezing.[14–16]

According to our unpublished data and previous studies the normal value of the rectal volume at maximum tolerable sensation for a child of six years is 135 mL and for an adult it is 240 mL.[17,18]

Defecometry

For this test the same types of catheter and the same patient position, *i.e.* sitting upright on a commode, were used as in the case of the balloon retention test. First, we filled the balloon with 50 mL of water of 37°C. We then asked the patient to evacuate the balloon. If the patient was unable to expel the balloon, we increased the volume into the balloon with 50 mL of water until the earlier measured urge sensation volume was reached. While the patient tried to evacuate the balloon, we measured the maximum rectal pressure, maximum anal sphincter pressure, and the time needed for evacuation. These variables provide insight into the parameters involved in the defecation process.[19] This test assesses whether the patient voluntarily contracts the external anal sphincter during defecation. If this is not the case, the patient suffers from dyssynergic defecation.

Earlier studies showed that normal subjects can expel a balloon filled with 100 mL of barium sulfate paste in a median of 7 seconds.[20] In our laboratory setting healthy subjects were able to expel the rectal balloon with 50 mL of water at body temperature. Failure to evacuate the balloon in one minute indicates an outlet obstruction which might possibly be caused by involuntary contraction of the external anal sphincter, otherwise known as dyssynergic defecation.[21]

Statistical analysis

The data was analyzed with SPSS 20.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY). We used Q-Q plots to determine whether the values were distributed normally. Subsequently, normally distributed values were reported as means with standard deviations and abnormally distributed values were reported as medians with minimum and maximum values, as appropriate.

RESULTS

During the three-year inclusion period we examined nine male and one female HD patient for severe constipation. The median age at the time of testing was 12 years and the range was 7 to 19 years. The mean duration of constipation was 4.0 ± 2.9 years; the shortest duration was six months and the longest nine years. All ten patients had histopathologically proven HD based on an absence of ganglion cells in both submucosal and myenteric plexuses as determined by rectal suction biopsies. One patient had an ultra-

short variant of HD based on the absence of ganglion cells at 3 cm on rectal suction biopsy and the absence of the rectoanal inhibitory reflex. This patient received conservative treatment in the form of laxatives. The nine other patients all had a rectosigmoid variant of HD and had received Duhamel pull-through procedures. We examined the pathology reports of the nine patients treated surgically and found that each report mentioned distal aganglionosis with sufficient ganglion cells in the proximal anastomosed surface. Post-operative complications were limited to three patients: one case of stenosis of the

Table 1
Anorectal function test results

Anal pressure profile (n = 10)	Median (Range)
Sphincter resting pressure (mm Hg)	70 (25 – 110)
Maximum sphincter squeezing pressure (mm Hg)	220 (140 – 380)

Defecometry (n = 10)	Median (Range)
Expulsion possible (n)	6/10
Expulsion volume (mL, n = 6)	75 (50 – 150)
Expulsion time (s, n = 6)	10 (5 – 40)
Maximum rectal pressure (mm Hg)	125 (70 – 185)
Maximum anal sphincter pressure (mm Hg)	185 (125 – 285)
Appropriate pelvic floor coordination (n)	0/10

Balloon retention test (n = 10)		Median (Range)
Basal rectal balloon pressure (mm Hg)		20 (10 – 25)
First sensation	Rectal balloon pressure (mm Hg)	30 (15 – 40)
Constant sensation	Rectal balloon volume (mL)	35 (10 – 295)
	Rectal balloon pressure (mm Hg, n=9)	35 (25 – 45)
	Rectal balloon volume (mL, n=9)	75 (25 – 205)
Urge sensation	Rectal balloon pressure (mm Hg, n=9)	35 (25 – 70)
	Rectal balloon volume (mL, n=9)	185 (70 – 565)
Maximum tolerable volume	Rectal balloon pressure (mm Hg)	40 (25 – 80)
	Rectal balloon volume (mL)	250 (80 – 845)
Rectal compliance until maximum tolerable volume (mL/mm Hg)		14 (2.6 – 77.0)

proximal anastomosis and two cases of anastomotic leakage. All three complications occurred directly following the surgical procedure and were treated subsequently. The time between the surgical corrections and subsequent complications and the anorectal function tests was 7, 9, and 17 years. The stenosis was treated with dilatation after which the symptoms decreased over time. The two cases of anastomotic leakage were treated with laparotomies combined with abdominal flushing and a temporary ileostomy in order to treat the persistent peritonitis. These two patients recovered fully during the course of several weeks. We found no statistically significant differences in the values between patients who had a post-operative complication and patients who experienced no post-operative complaints. Two patients experienced an episode of Hirschsprung's associated enterocolitis, one pre-operative and the other post-operative. All ten patients used laxatives and/or had enemas to cope with their constipation at the time the diagnoses were made. None of the patients had severe comorbidities troubling their defecation, apart from one patient who had Down's syndrome. This patient had a mild form of mental retardation and was capable of understanding the tasks involved in the anorectal function tests.

The anal pressure profile results showed an increased anal sphincter resting pressure with a median value of 70 mm Hg and a maximum squeezing pressure median of 220 mm Hg (Table 1). Furthermore, we found that in all ten patients the rectoanal inhibition reflex was absent, confirming their initial diagnosis of HD.

The defecometry test results showed that four out of ten patients completely failed to expel the balloon. And, in the event of expulsion, patients either required more volume or more time in order to succeed (Table 1 and Figure 2). Vastly increased pressures were seen in both the rectum and the anal sphincter (Table 1). This combination of sufficient propulsive force and increased anal pressure while squeezing led to the diagnosis of dyssynergic defecation. Proper coordination of defecation was absent in all ten patients we tested by means of defecometry.

The balloon retention test results showed that overall increased volumes were required to sense the balloon. We measured an increased first sensation volume of 295 mL in one patient and 150 mL in another, while normal values range from 30 mL to 50 mL depending on the patient's age. We found serious enlargement of the rectum in two patients with maximum tolerable volume values of 600 mL and 845 mL (Table 1). We found overall enlargement in eight out of ten patients (Figure 3). One patient failed to notice constant sensation and urge sensation but he did notice the maximum tolerable volume of 600 mL.

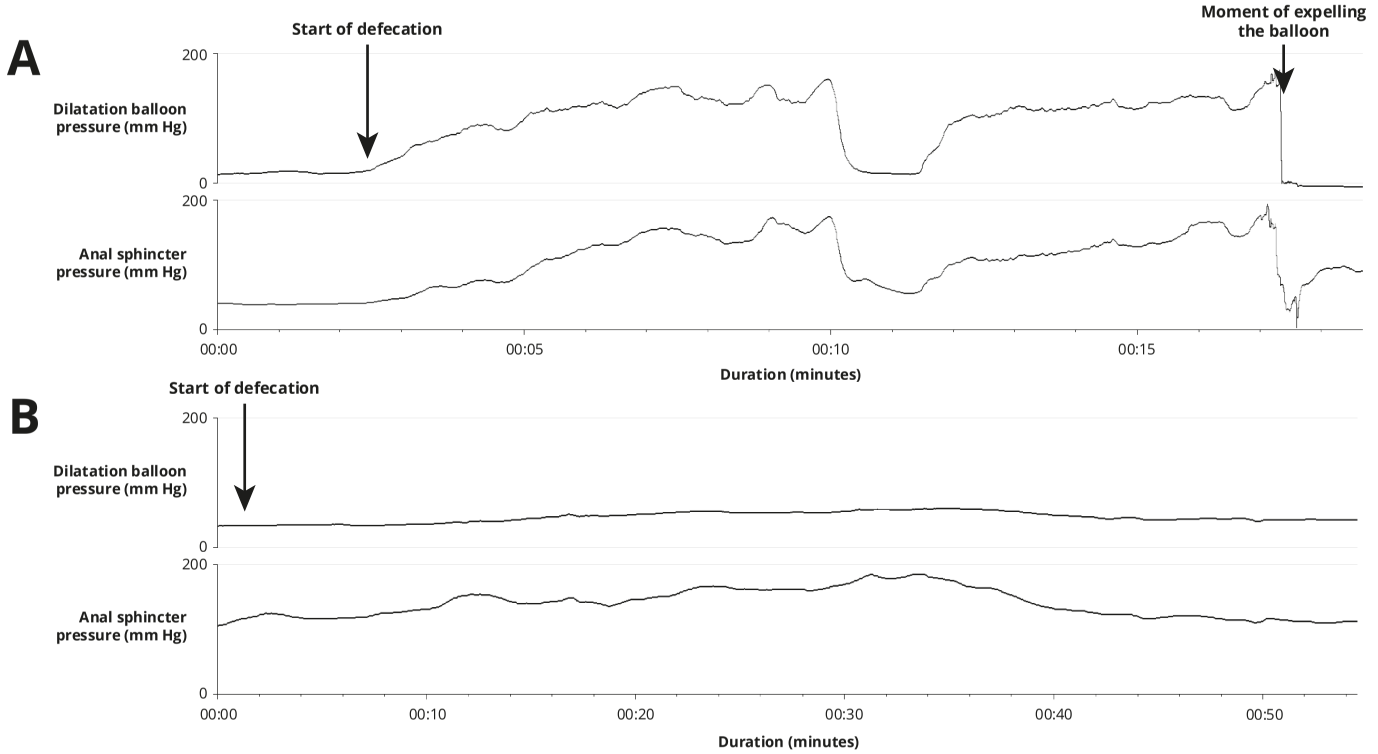

Figure 2

Anal pressure profiles of two patients with dyssynergic defecation.

A: The first patient was able to expel the rectal balloon despite contracting the anal sphincter.

B: The second patient failed to expel the rectal balloon due to heavy contraction of the anal sphincter.

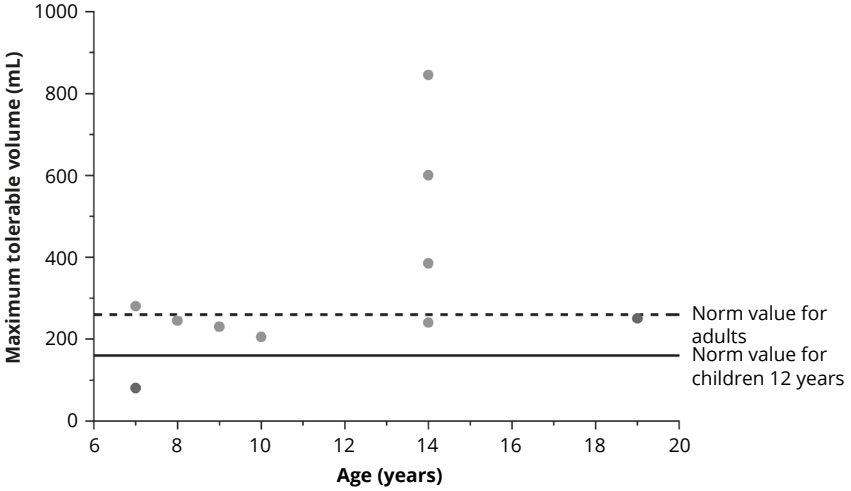

Figure 3

Maximum tolerable volume measurements of all ten patients at the age of diagnosis. The black line represents the normal value for children of 12 years of age (160 mL). The dotted line represents the normal value for adults (260 mL).

DISCUSSION

While most post-operative HD patients have good clinical outcomes and do not suffer from severe defecation complaints, a substantial number of patients seem to struggle with ongoing severe constipation.[6–9] One could argue that this is possibly caused by residual aganglionosis following surgical correction in patients treated for HD. Nevertheless, the appearance and number of ganglion cells in the proximal anastomosed surface was normal in all nine patients in our study who had been treated surgically. This meant that resection had been adequate. On the basis of rectal suction biopsies, the tenth patient was treated conservatively with laxatives for his ultra-short variant of HD. While this diagnosis, along with its treatment possibilities, remains undetermined,[22] pelvic muscle control was still completely absent in this patient. This pointed to dyssynergic defecation. In all ten patients the rectoanal inhibition reflex was absent as is seen in HD.[23] Consequently, all patients were, by definition, slightly constipated. Nevertheless, absence of this reflex does not explain why a substantial number of the post-operative HD patients suffer from more severe complaints than others, as the rectoanal inhibitory reflex is absent in all HD patients. We demonstrated that a piece of this complex puzzle could be dyssynergic defecation aggravating the already troublesome defecation. Following defecometry we diagnosed all ten patients in our study with dyssynergic defecation. This meant that in addition to a non-relaxing internal anal sphincter the external anal

sphincter of these patients also contracted paradoxically during defecation. While most constipation complaints in HD patients are attributed to the disease itself, it is possible that a significant number of HD patients have never mastered the act of defecation properly and, consequently, these patients have dealt with dyssynergic defecation since early childhood. While hard evidence for this theory is still lacking, the extremely enlarged rectums we found in two patients seem to indicate long-standing constipation caused by dyssynergic defecation.

Several reasons for the onset of dyssynergic defecation have been described and one of these factors could be responsible for its onset in post-operative HD patients. Firstly, Rao *et al* suggested that the onset of dyssynergic defecation symptoms during childhood, in otherwise healthy patients, may be due to faulty learning of proper defecation.[12] Secondly, Hyman suggested that pain in the rectum after surgery and washouts may lead to patients avoiding bowel movement as these are often associated with increased pain.[13] A third and final possibility might be that post-operative complications or Hirschsprung's associated enterocolitis could make patients more prone to developing dyssynergic defecation, especially since these are associated with additional treatment and sometimes even with a redo of the surgical procedure. Our results showed that three out of ten patients (30%) had a post-operative complication. Even though this is a relatively high number, the small number of patients in our study makes it difficult to statistically define post-operative complications as the pre-determining factor for dyssynergic defecation. It still remains unclear whether dyssynergic defecation in HD patients with severe complaints is caused by congenital disease, surgical correction for HD, or that it develops at a much later age regardless of the patients' medical history. Moreover, further research on a non-selected cohort of both adequately and poorly functioning HD patients is necessary to determine the exact incidence of dyssynergic defecation in the entire HD disease population.

Persistent constipation due to dyssynergic defecation was shown to have a negative influence on overall quality of life as it significantly impairs social life, sex life, work life, and family relationships.[12] Our data demonstrated the added risk of serious enlargement of the rectum with decreased elasticity of the rectal wall due to long-standing constipation caused by dyssynergic defecation. We found one patient who measured a maximum tolerable volume of 845 mL at the age of ten years. Absence of the rectoanal inhibitory reflex, as is seen in HD, will probably lead to a slight increase in rectal volume in all patients. Some of these values are so vastly increased, however, that they are too high even for HD. Moreover, dyssynergic defecation in HD patients may initiate a vicious circle of fear of pain during defecation and defecation avoidance behavior that may eventually cause overflow incontinence.

Nowadays, dyssynergic defecation is treated with a high fiber diet, laxatives, and biofeedback training.[24] Several reports already recognize the positive effects of biofeedback therapy on constipation in non-HD patients.[25–29] Besides improving the defecation process, biofeedback training reportedly also improves overall quality of life.[30] One case report showed that biofeedback training has great potential for patients with constipation and fecal seepage in the presence of HD.[31] In other colorectal diseases, such as inflammatory bowel diseases, dyssynergic defecation was shown to be treatable by biofeedback therapy.[11] This also points out the great potential of this therapy in HD patients with severe constipation. Further research on the effects of biofeedback training in this relatively young group of patients, who have dyssynergic defecation in addition to HD, is in progress. It will have to show to what extent it is possible to treat the complaints characteristic of this particular group of patients.

Conclusions

It is important to consider the diagnosis of dyssynergic defecation when dealing with severe constipation in post-operative HD patients. Our results show that a number of HD patients have problems with wrongly contracting their external anal sphincters, in addition to a non-relaxing internal anal sphincter characteristic for HD. If dyssynergic defecation is diagnosed at an early age, viable treatment options are available that may prevent irreversible long-term complications, such as significant enlargement of the rectum and, eventually, overflow incontinence.

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REFERENCES

1 Spouge D, Baird PA. Hirschsprung disease in a large birth cohort. Teratology. 1985;32:171–7.
2 Suita S, Taguchi T, Ieiri S, et al. Hirschsprung's disease in Japan: analysis of 3852 patients based on a nationwide survey in 30 years. J Pediatr Surg. 2005;40:197–201.
3 Baillie CT, Kenny SE, Rintala RJ, et al. Long-term outcome and colonic motility after the Duhamel procedure for Hirschsprung's disease. J Pediatr Surg. 1999;34:325–9.
4 Yanchar NL, Soucy P. Long-term outcome after Hirschsprung's disease: patients' perspectives. J Pediatr Surg. 1999;34:1152–60.
5 Catto-Smith AG, Trajanovska M, Taylor RG. Long-term continence after surgery for Hirschsprung's disease. J Gastroenterol Hepatol. 2007;22:2273–82.
6 Shono K, Hutson JM. The treatment and postoperative complications of Hirschsprung's disease. Pediatr Surg Int. 1994;9:362–5.
7 Menezes M, Corbally M, Puri P. Long-term results of bowel function after treatment for Hirschsprung's disease: a 29-year review. Pediatr Surg Int. 2006;22:987–90.
8 Jarvi K, Laitakari EM, Koivusalo A, et al. Bowel function and gastrointestinal quality of life among adults operated for Hirschsprung disease during childhood: a population-based study. Ann Surg. 2010;252:977–81.
9 Chumpitazi BP, Nurko S. Defecation disorders in children after surgery for Hirschsprung disease. J Pediatr Gastroenterol Nutr. 2011;53:75–9.
10 Rao SS, Welcher KD, Leistikow JS. Obstructive defecation: a failure of rectoanal coordination. Am J Gastroenterol. 1998;93:1042–50.
11 Perera LP, Ananthakrishnan AN, Guilday C, et al. Dyssynergic defecation: a treatable cause of persistent symptoms when inflammatory bowel disease is in remission. Dig Dis Sci. 2013;58:3600–5.
12 Rao SS, Tuteja AK, Vellema T, et al. Dyssynergic defecation: demographics, symptoms, stool patterns, and quality of life. J Clin Gastroenterol. 2004;38:680–5.
13 Hyman PE. Defecation disorders after surgery for Hirschsprung's disease. J Pediatr Gastroenterol Nutr. 2005;41 Suppl 1:S62-3.
14 Penninckx FM, Lestar B, Kerremans RP. A new balloon-retaining test for evaluation of anorectal function in incontinent patients. Dis Colon Rectum. 1989;32:202–5.
15 Broens PM, Penninckx FM, Lestar B, et al. The trigger for rectal filling sensation. Int J Colorectal Dis. 1994;9:1–4.
16 Broens P, Vanbeckevoort D, Bellon E, et al. Combined radiologic and manometric study of rectal filling sensation. Dis Colon Rectum. 2002;45:1016–22.
17 Broens PM, Penninckx FM. Relation between anal electrosensitivity and rectal filling sensation and the influence of age. Dis Colon Rectum. 2005;48:127–33.
18 Fathy A, Megahed A, Barakat T, et al. Anorectal functional abnormalities in Egyptian children with chronic functional constipation. Arab J Gastroenterol. 2013;14:6–9.
19 Lestar B, Penninckx FM, Kerremans RP. Defecometry. A new method for determining the parameters of rectal evacuation. Dis Colon Rectum. 1989;32:197–201.
20 Kamm MA, Bartram CI, Lennard-Jones JE. Rectodynamics--quantifying rectal evacuation. Int J Colorectal Dis. 1989;4:161–3.
21 Rao SS. Dyssynergic defecation. Gastroenterol Clin North Am. 2001;30:97–114.
22 Puri P, Gosemann JH. Variants of Hirschsprung disease. Semin Pediatr Surg. 2012;21:310–8.
23 Callaghan RP, Nixon HH. Megarectum: Physiological Observations. Arch Dis Child.

1964;39:153–7.
24 Rao SS. Dyssynergic defecation and biofeedback therapy. Gastroenterol Clin North Am. 2008;37:569–86, viii.
25 Chiarioni G, Whitehead WE, Pezza V, et al. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. Gastroenterology. 2006;130:657–64.
26 Heymen S, Scarlett Y, Jones K, et al. Randomized, controlled trial shows biofeedback to be superior to alternative treatments for patients with pelvic floor dyssynergia-type constipation. Dis Colon Rectum. 2007;50:428–41.
27 Hak NG, El-Hemaly M, Hamdy E, et al. Pelvic floor dyssynergia: efficacy of biofeedback training. Arab J Gastroenterol. 2011;12:15–9.
28 Hart SL, Lee JW, Berian J, et al. A randomized controlled trial of anorectal biofeedback for constipation. Int J Colorectal Dis. 2012;27:459–66.
29 Koh D, Lim JF, Quah HM, et al. Biofeedback is an effective treatment for patients with dyssynergic defaecation. Singapore Med J. 2012;53:381–4.
30 Zhu FF, Lin Z, Lin L, et al. Changes in quality of life during biofeedback for people with puborectalis dyssynergia: generic and disease-specific measures. J Adv Nurs. 2011;67:1285–93.
31 Tantiphlachiva K, Rao S. Biofeedback therapy for bowel problems in adults after surgical treatment for childhood Hirschsprung's disease. Dev Neurorehabil. 2009;12:442–9.

CHAPTER 11

General discussion and future perspectives

At the beginning of this thesis, we formulated two aims. Our first aim was to improve the diagnostic process in Hirschsprung's disease (HD), aiming to increase the accuracy and to reduce the number of invasive biopsy procedures. Our second aim was to assess long-term outcomes in HD with regard to both functional outcomes and quality of life. The studies reported in this thesis have provided new insights into both the diagnostic process and the long-term outcomes of HD. In this chapter, we will reflect on the hypotheses formulated in the course of this research, discuss the clinical implications, and propose directions for future research.

EARLY DIAGNOSIS

The current most commonly used method for the diagnosis of HD is the rectal suction biopsy.[1] A study by Bagdzevicius and colleagues, however, recently pointed out that the rectal suction biopsy may not be an entirely satisfactory method for diagnosing HD, since its outcome may be affected by the patient's age.[2] Furthermore, in our everyday clinical work we also observed that the diagnosis of HD by rectal suction biopsy was often very problematic in newborns. On the basis of this clinical experience, combined with knowledge from the scientific literature, we set out to investigate what caused this problematic diagnostic process and how we could improve it.

Accuracy of the rectal suction biopsies

At the beginning of **Chapter 2**, we hypothesized that the accuracy of rectal suction biopsies in the diagnosis of HD might be influenced by patient age. In point of fact, the results did demonstrate that patient age had a bearing on the accuracy of the outcome of the rectal suction biopsy. The sensitivity, that is the true positive rate, of rectal suction biopsy outcomes, in particular, was significantly lower when the biopsies were obtained in patients younger than 39 days. In contrast, the specificity, that is the true negative rate, of rectal suction biopsy outcomes was not influenced by age and remained high (95%) in all the age groups we investigated. We believe that the influence of age on the sensitivity results from the immaturity of the enteric nervous system, more specifically a delayed proliferation of nerve fibers, which are still dynamically developing and therefore quickly changing after birth. Nakao and colleagues also noted this aspect,[3] demonstrating that nerve fibers continue to proliferate even after a child is born with HD. Thus, the developmental characteristics of the enteric nervous system, as related to changes in the density of nerve fibers, result in a different staining pattern in younger patients before the classic pattern, which is characteristic of HD as seen in older patients, has had time to develop.[4] This, in turn, causes the rectal suction biopsy to be less reliable in patients

younger than 39 days, as our results showed.

Translated to daily clinical experience, these results indicate that performing rectal suction biopsies in patients younger than 39 days should be avoided, and, if the biopsies obtained below this age are negative or inconclusive for HD, they should be repeated if the symptoms of the patient persist.

Complementing the rectal suction biopsy with anorectal manometry

Aside from lower accuracy in very young patients, there also remains a small risk of complications such as rectal bleeding because of the invasive nature of the rectal suction biopsy.[5,6] Moreover, the results presented in **Chapter 2** also show that 17% of the biopsies need to be repeated due to inconclusive test results. A less invasive tool should therefore preferably be used, to reduce the number of invasive biopsy procedures. Such a tool could be anorectal manometry, which can be used to measure rectoanal reflexes by dilating a rectal balloon and measuring the response in anal sphincter pressure. In healthy individuals, rectal balloon distention evokes a short relaxation of the internal anal sphincter called the rectoanal inhibitory reflex (RAIR),[7] whereas in patients with HD this reflex is absent.[8–10] Following this line of reasoning, a RAIR found by using anorectal manometry obviates the need for an invasive biopsy procedure, since HD has virtually been excluded. Unfortunately, in the past, performing anorectal manometry in very young patients was disputed because of the difficulties involved.[1,11] As a consequence, only a small percentage of pediatric surgeons still use anorectal manometry in the diagnosis of HD, while the majority opt for rectal suction biopsy as the diagnostic of first choice.[12,13] In recent years, however, modifications to our anorectal manometry protocol have helped us to increase its diagnostic accuracy. More specifically, by setting strict criteria for the evaluation of the RAIR, we believe we have increased the sensitivity of anorectal manometry, while at the same time sacrificing some of its specificity.

Based on this, we hypothesized prior to **Chapter 3** that, with the right modifications, anorectal manometry could be used to reduce the number of invasive biopsies needed to exclude HD. The results of this study show that anorectal manometry scored equally well with respect to the diagnostic aspects of sensitivity and negative predictive value, whereas it scored significantly worse with respect to the aspects of specificity and positive predictive value. Nevertheless, we demonstrated that by correctly modifying the anorectal manometry protocol, performance on these aspects could be improved.

Importantly, no false negative results were obtained using anorectal manometry. Clinically, this implicates that a functioning RAIR detected with anorectal manometry excludes HD with absolute certainty. This could benefit young patients with constipation, since they would be spared undergoing an invasive biopsy procedure. In contrast, the false

positive anorectal manometry results do mean that at all times it remains necessary to perform a rectal suction biopsy in case no RAIR was found through anorectal manometry, especially since the diagnosis of HD in most cases implies a major surgical intervention.

Further advantages of anorectal manometry

In **Chapter 3**, we demonstrated that anorectal manometry can be a valuable tool in the evaluation of pediatric patients with constipation, since it has the potential to reduce the number of rectal suction biopsies needed to exclude HD. Aside from its value in the diagnosis of HD, anorectal manometry can also serve as a complement to rectal suction biopsy in the diagnosis of other causes of constipation in infants and children. For example, in this chapter we found patients in whom HD had been excluded by rectal suction biopsy but who still had an absence of the RAIR during anorectal manometry. We hypothesized that in this group of patients, where HD had been excluded, absence or immaturity of the RAIR could be an explanation for their severe constipation. In fact, the results of **Chapter 4** show that, in a limited number of patients, immaturity of the RAIR might indeed play a role in the constipation seen in these patients. Consequently, constipation in these patients may well decrease as the functioning of the RAIR matures further.

The results of **Chapter 4** could provide a valuable explanation for severe constipation in newborns, whose other tests, such as rectal suction biopsy, are negative. These findings warrant some refection. While anorectal manometry and absence of the RAIR offer a potential explanation for the constipation symptoms in these young patients, they may not provide a clear prognosis with regard to the constipation. For example, not all patients in our study had a fully matured RAIR at the end of the study, and nearly all patients still required laxatives and/or rectal irrigation. Additionally, some patients may suffer from a disorder called internal anal sphincter achalasia,[14] previously referred to as ultrashort segment HD, which is characterized by a permanent absence of the RAIR and a persistent tendency towards constipation. Thus, the direct clinical implications related to the knowledge that a patient has an immature or absent RAIR are currently hampered, because it is still impossible to distinguish patients whose RAIR might further maturate from patients whose RAIR will not maturate and who will thus retain a lifelong tendency towards constipation. Moreover, with the knowledge at our disposal now, we do not know how to evoke or stimulate any such maturation of RAIR. Additional research is needed to further explore the maturation of the RAIR, and to identify risk factors for favorable or unfavorable outcomes.

In summary and clinical implications

The aim of the first part of this thesis was to improve the diagnostic process of HD, primarily in terms of increasing the accuracy and reducing the number of invasive biopsy procedures. We believe the first chapters of this thesis, **Chapters 2 through 4**, provide new insights that can be used to achieve this aim. To summarize the results of these chapters, we drew up a new flowchart to be used in newborns with constipation who are suspected of having HD (Figure 1). Ideally, newborns and infants with severe constipation should initially be investigated using anorectal manometry, paying close attention to the functioning of the RAIR by applying the lessons we learned on anorectal manometry in **Chapter 3**. On the basis of the functioning of the RAIR, the next step should be either a conservative treatment (possibly combined with investigations for other causes of constipation), or a rectal suction biopsy to confirm or exclude the diagnosis of HD. If the biopsy confirms the diagnosis of HD, a surgical treatment may be performed based on the patient's complaints and length of aganglionosis. If the biopsy shows no abnormalities, an immature RAIR can be the cause of the constipation, and conservative treatment using laxatives and rectal washouts needs to be started. A follow-up anorectal manometry measurement should be performed to monitor the maturation of the RAIR, since **Chapter 4** shows that maturation of this reflex may reduce constipation.

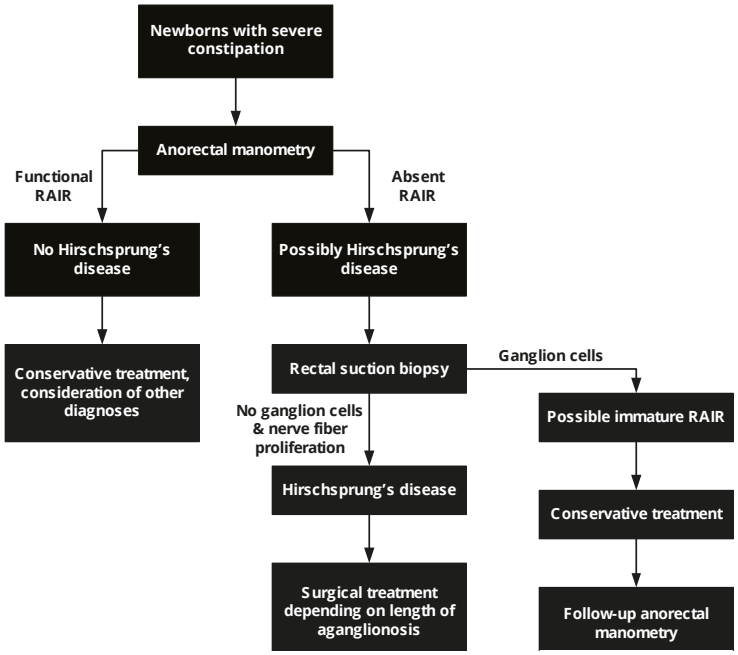

Figure 1

Newly proposed diagnostic algorithm.

LONG-TERM OUTCOMES

Following diagnosis, the majority of HD patients undergo surgery to resect the affected intestines and restore bowel continuity. Despite the best surgical efforts, multiple studies have emphasized that HD is not a curable disease, which is illustrated by various reports showing that a large proportion of patients continue to suffer from functional complaints, such as constipation and fecal incontinence, following surgery.[15–20] To date, it is not exactly clear why some patients experience more difficulties than others. With this in mind, we set out to assess the long-term outcomes of HD, with regard to both functional outcomes and quality of life (QoL). By doing so, we hoped to identify those factors that cause some patients to experience more difficulties than others, and therefore establish starting points for improving long-term outcomes in HD.

Overall functional outcomes and quality of life

In **Chapter 8**, the results of a nationwide cross-sectional study involving long-term outcomes in HD were described.

Interestingly, the prevalence of constipation in HD patients did not differ significantly from the control group. The severity of constipation, however, was greater in HD patients than in the control group, as indicated by a higher prevalence of various constipation complaints, and a higher usage of laxatives and rectal irrigation in HD patients. This was to be expected, since even after surgical reconstruction HD patients inherently retain a tendency towards constipation, possibly due to the persistent absence of the RAIR or residual aganglionosis.

In contrast to the prevalence of constipation, we did find that HD patients suffer significantly more often from impaired fecal continence, in particular fecal soiling, when compared to the controls. The prevalence of fecal incontinence was 37.6% in the pediatric HD population and 16.8% in the adult HD population. These rates are comparable to those found by other studies, such as the 39% prevalence reported by Catto-Smith and colleagues.[21] A more recent study by Neuvonen and colleagues demonstrated that fecal incontinence would eventually diminish to a prevalence level not significantly different from that of healthy controls, even though soiling persisted in well over 40% of their adult subgroup.[22] It therefore seems that fecal continence may improve with age, but that symptoms of incontinence persist well into adulthood. Some authors postulated that fecal incontinence in these patients may result from impaired functioning of the anal sphincter following surgery or from a reduced rectal reservoir as a result of surgical reconstruction.[23] Apart from these factors, our results also showed that patients who required a redo pull-through procedure were significantly more likely to suffer from fecal

incontinence. It remains unclear to what extent the redo procedure itself contributes to the increase in fecal incontinence complaints, since these patients may already have been worse off prior to their redo procedure. Clinically, however, these results do mean that, while a redo procedure may ultimately be necessary in some patients, one should be cautious about promising favorable functional outcomes, because the prevalence of fecal incontinence in patients after redo remains high.

In terms of QoL, our results showed that especially pediatric HD patients had significantly lower QoL domain scores compared to the reference data. These lower QoL domain scores may partially be explained by functional complaints, since we found a negative and moderate relationship between several QoL domains and constipation. One positive point that could be observed from these results was that the influence of functional complaints on QoL had diminished in adult HD patients, since adult patients scored higher in all four tested domains that describe different aspects of QoL compared to their respective reference data. One possible explanation for this finding may be that adult patients have developed better coping strategies. Adults may have more options for adapting their lives to accommodate any functional complaints, whereas children are often constrained by set activities such as school or afterschool commitments.

Despite the favorable QoL outcomes in adult patients, they still suffer significantly more often from fecal incontinence compared to their control group. We believe that these results are an indication that counselling and transitional care are necessary for adult patients who continue to have functional complaints as they grow older.

Comparison of surgical techniques

A factor that could influence the long-term outcomes of patients with HD is the choice of surgical technique used for the resection of aganglionic intestines. In the majority of Dutch HD patients, the resection is done by either a Duhamel procedure or transanal endorectal pull-through (TERPT) procedure.[24,25] Multiple studies have compared the outcomes of the two procedures, often with varying results and often based on small heterogeneous patient groups.[26–29] A major flaw in these studies is the difference in age of the two groups being compared, which results from the use of different patient cohorts and which subsequently biases the results. A recent meta-analysis by Chen and colleagues indeed showed that the current quality of evidence is too poor to draw any conclusions as to the comparison of both techniques.[30] Given the nature of both procedures, we hypothesized that there might be an increased prevalence of fecal incontinence following the TERPT procedure because of overt stretching of the anal sphincter, whereas the Duhamel procedure may be followed by an increase in constipation complaints because of the residual aganglionic rectum.

Indeed, the results of a matched comparison of both procedures described in **Chapter 9** confirm that patients who underwent a Duhamel procedure had an increased tendency towards constipation compared to patients who underwent a TERPT procedure. This difference in outcomes may result from structural differences in both surgical techniques, since it has been postulated that the pouch created in the Duhamel procedure, partially consisting of the native aganglionic rectum, may continue to impair bowel function, thus leading to an increased tendency to constipation.[31]

Contrary to what we hypothesized, there was no significant difference in the prevalence of fecal incontinence or in the prevalence of urinary incontinence following a Duhamel or TERPT procedure. Importantly, we found that fecal continence may be further improved by avoiding the completely transanal approach during TERPT procedure and, instead, opting for assisting the TERPT with laparotomy or laparoscopy. This finding contradicts a previous meta-analysis by Thomson and colleagues,[32] which did not reveal any differences between the two approaches. It must be noted, however, that all the studies included were retrospective case studies and that the authors of the meta-analysis themselves concluded that the overall quality of the studies was poor. In any case, it is simply not possible to draw any conclusion regarding the exact cause of the difference in fecal continence between the two TERPT approaches in our current study. The reduced visibility of anatomical structures during the completely transanal approach may increase the risk of iatrogenic pelvic nerve damage, thus resulting in a higher risk of impaired continence. Another cause of impaired continence may be the prolonged stress on the anal sphincter during the completely transanal approach.

The study presented in **Chapter 9** indicates that the differences in functional outcomes following the Duhamel and TERPT procedures, when they do occur, are small. That said, we believe further studies are necessary to investigate what causes the differences between the procedures. Such studies should include extensive anorectal manometric investigations that can compare the anorectal physiological functioning between patients treated by either the Duhamel or TERPT procedure.

Dyssynergic defecation in patients with Hirschsprung's disease

As HD patients grow older, functional complaints may inherently persist, since the results described in **Chapter 6** show that, even in the healthy general population, constipation and fecal incontinence are common complaints. Apart from HD, other factors, such as poor diet, could play an increasingly important role in the constipation complaints of older HD patients.[33] Another cause of constipation in older HD patients could be dyssynergic defecation, a disorder characterized by a paradoxical involuntary contraction of the external anal sphincter and/or puborectal muscle, which leads to a

functional neuromuscular obstruction.[34] While the exact cause of dyssynergic defecation is unknown for the majority of patients affected, its development during childhood, pregnancy, and trauma have been identified as possible causes that might set off these defecation problems.[35] It could therefore be possible that some HD patients, in addition to being unable to relax their internal anal sphincter, might have the additional problem of their external anal sphincter and puborectal muscle involuntarily contracting during defecation.

Taking all this into consideration, we hypothesized at the start of **Chapter 10** that not all post-operative defecation complaints were attributable to HD and that dyssynergic defecation – for which viable treatment options are available – may increase the severity of constipation in these patients. Following defecometry, a test used to simulate the act of rectal evacuation, we found that all ten of the HD patients with severe constipation following surgical reconstruction that we investigated also had symptoms of dyssynergic defecation. We were unable to explain the etiology of the inappropriate pelvic floor muscle usage found in these patients; various causes are feasible. First, some patients may experience dyssynergic defecation due to faulty learning of proper defecation during childhood.[35] Second, pain in the rectum after surgery and washouts may cause patients to try to avoid regular bowel movements, as these are often associated with increased pain.[36] Finally, it is possible that post-operative complications or Hirschsprung's associated enterocolitis could make some patients more prone to develop dyssynergic defecation, especially since these are often associated with additional treatment and sometimes even with a redo of the surgical procedure.

Clinically, this means that it is important to consider the diagnosis of dyssynergic defecation when dealing with severe constipation in post-operative HD patients, especially since there are viable treatment options available that may prevent irreversible long-term complications such as significant enlargement of the rectum and, eventually, overflow incontinence. Further research is necessary to determine the exact cause of the dyssynergic defecation in HD patients with severe constipation. Moreover, further research on a non-selected cohort of both adequately and poorly functioning HD patients is necessary to determine the exact incidence of dyssynergic defecation in the entire HD disease population.

FUTURE PERSPECTIVES

As stated throughout this discussion, much research remains to be done in terms of both the diagnostic process in patients suspected of HD and the long-term outcomes of HD.

For instance, the diagnosis of conditions related to HD, such as internal sphincter

achalasia or immaturity of the RAIR, remains unclear. While we have shown that the RAIR may indeed further mature in some newborns with constipation, it is still unclear how this process fully works. Future studies in this group of patients should therefore entail a longitudinal study design with multiple anorectal manometry measurements at fixed ages, combined with measurements from a control group without constipation complaints.

Moreover, while our nationwide cross-sectional study on the long-term outcomes of HD provided us with an unprecedented high number of patients, longitudinal studies would be preferable in order to study the influence of aging on functional complaints and QoL. Repetition of our study in five or ten years, using the same cohort of patients, might create the conditions for performing such a longitudinal analysis.

The results of this thesis furthermore indicate that the differences between the various surgical techniques for HD, if any, are small. It is important to note, however, that further investigations that include anorectal manometry are necessary to accurately compare anorectal functioning between patients treated by either procedure. These measurements may also indicate the incidence of dyssynergic defecation in the entire HD disease population.

CONCLUSION

The work described in this thesis has provided new insights into the early diagnosis and long-term outcomes of HD. The diagnosis of HD has vastly improved over the past few decades, and the work done in the course of this thesis may help further reduce the number of invasive biopsies needed for diagnosis, thus reducing the risk of complications in this young group of patients. Additionally, the studies performed for this thesis involving the long-term outcomes of HD have helped further elucidate why some patients may have more complaints than others. This, in turn, has opened up new possibilities for future research and treatment.

REFERENCES

1 Lorijn F De, Kremer LCM, Reitsma JB, et al. Diagnostic Tests in Hirschsprung Disease : A Systematic Review. J Pediatr Gastroenterol Nutr. 2006;42:496–505.

2 Bagdzevicius R, Gelman S, Gukauskiene L, et al. Application of acetylcholinesterase histochemistry for the diagnosis of Hirschsprung's disease in neonates and infants: a twenty-year experience. Medicina (Kaunas). 2011;47:374–9.

3 Nakao M, Suita S, Taguchi T, et al. Fourteen-year experience of acetylcholinesterase staining for rectal mucosal biopsy in neonatal Hirschsprung's disease. J Pediatr Surg. 2001;36:1357–63.

4 Santos MM, Tannuri U, Coelho MC. Study of acetylcholinesterase activity in rectal suction biopsy for diagnosis of intestinal dysganglionoses: 17-year experience of a single center. Pediatr Surg Int. 2008;24:715–9.

5 Pini-Prato A, Martucciello G, Jasonni V. Rectal suction biopsy in the diagnosis of intestinal dysganglionoses: 5-year experience with Solo-RBT in 389 patients. J Pediatr Surg. 2006;41:1043–8.

6 Friedmacher F, Puri P. Rectal suction biopsy for the diagnosis of Hirschsprung's disease: a systematic review of diagnostic accuracy and complications. Pediatr Surg Int. 2015;31:821–30.

7 Bharucha AE. Pelvic floor: anatomy and function. Neurogastroenterol Motil. 2006;18:507–19.

8 Schnaufer L, Talbert JL, Haller JA, et al. Differential sphincteric studies in the diagnosis of ano-rectal disorders of childhood. J Pediatr Surg. 1967;2:538–43.

9 Lawson JO, Nixon HH. Anal canal pressures in the diagnosis of Hirschsprung's disease. J Pediatr Surg. 1967;2:544–52.

10 Scharli AF. Pathophysiology of Classical Hirschsprung's disease. In: Holschneider AM, Puri P, editors. Hirschsprung's Disease and Allied Disorders. Frankfurt, Germany: Springer; 2000. p. 109–25.

11 Iwai N, Yanagihara J, Tokiwa K, et al. Reliability of anorectal manometry in the diagnosis of Hirschsprung's disease. Z Kinderchir. 1988;43:405–7.

12 Bradnock TJ, Knight M, Kenny S, et al. Hirschsprung's disease in the UK and Ireland: incidence and anomalies. Arch Dis Child. 2017;102:722-7.

13 Zani A, Eaton S, Morini F, et al. European Paediatric Surgeons' Association Survey on the Management of Hirschsprung Disease. Eur J Pediatr Surg. 2016;27:96–101.

14 Puri P, Gosemann JH. Variants of Hirschsprung disease. Semin Pediatr Surg. 2012;21:310–8.

15 Heij HA, de Vries X, Bremer I, et al. Long-term anorectal function after Duhamel operation for Hirschsprung's disease. J Pediatr Surg. 1995;30:430–2.

16 Menezes M, Corbally M, Puri P. Long-term results of bowel function after treatment for Hirschsprung's disease: a 29-year review. Pediatr Surg Int. 2006;22:987–90.

17 Ieiri S, Nakatsuji T, Akiyoshi J, et al. Long-term outcomes and the quality of life of Hirschsprung disease in adolescents who have reached 18 years or older—a 47-year single-institute experience. J Pediatr Surg. 2010;45:2398–402.

18 Jarvi K, Laitakari EM, Koivusalo A, et al. Bowel function and gastrointestinal quality of life among adults operated for Hirschsprung disease during childhood: a population-based study. Ann Surg. 2010;252:977–81.

19 Aworanti OM, McDowell DT, Martin IM, et al. Does Functional Outcome Improve with Time

Postsurgery for Hirschsprung Disease? Eur J Pediatr Surg. 2015;26:192–9.
20 Niramis R, Watanatittan S, Anuntkosol M, et al. Quality of life of patients with Hirschsprung's disease at 5 - 20 years post pull-through operations. Eur J Pediatr Surg. 2008;18:38–43.
21 Catto-Smith AG, Trajanovska M, Taylor RG. Long-term continence after surgery for Hirschsprung's disease. J Gastroenterol Hepatol. 2007;22:2273–82.
22 Neuvonen MI, Kyrklund K, Rintala RJ, et al. Bowel Function and Quality of Life After Transanal Endorectal Pull-through for Hirschsprung Disease: Controlled Outcomes up to Adulthood. Ann Surg. 2017;265:622–9.
23 Heikkinen M, Rintala RJ, Louhimo I. Bowel function and quality of life in adult patients with operated Hirschsprung's disease. Pediatr Surg Int. 1995;10:342–4.
24 Duhamel B. A new operation for the treatment of Hirschsprung's disease. Arch Dis Child. 1960;35:38–9.
25 la Torre-Mondragón L De, Ortega-Salgado JA. Transanal endorectal pull-through for Hirschsprung's disease. J Pediatr Surg. 1998;33:1283–6.
26 Martins ECS, Peterlini FL, Fagundes DJ, et al. Clinical, manometric and profilometric evaluation after surgery for Hirschsprung's disease: comparison between the modified Duhamel and the transanal rectosigmoidectomy techniques. Acta Cir Bras. 2009;24:416–22.
27 Tannuri ACA, Tannuri U, Romão RLP. Transanal endorectal pull-through in children with Hirschsprung's disease—technical refinements and comparison of results with the Duhamel procedure. J Pediatr Surg. 2009;44:767–72.
28 Gunnarsdóttir A, Larsson LT, Arnbjörnsson E. Transanal Endorectal vs. Duhamel Pull-Through for Hirschsprung's Disease. Eur J Pediatr Surg. 2010;20:242–6.
29 Giuliani S, Betalli P, Narciso A, et al. Outcome Comparison Among Laparoscopic Duhamel, Laparotomic Duhamel, and Transanal Endorectal Pull-Through: A Single-Center, 18-Year Experience. J Laparoendosc Adv Surg Tech. 2011;21:859–63.
30 Chen Y, Nah SA, Laksmi NK, et al. Transanal endorectal pull-through versus transabdominal approach for Hirschsprung's disease: A systematic review and meta-analysis. J Pediatr Surg. 2013;48:642–51.
31 Lawal TA, Chatoorgoon K, Collins MH, et al. Redo pull-through in Hirschprung's disease for obstructive symptoms due to residual aganglionosis and transition zone bowel. J Pediatr Surg. 2011;46:342–7.
32 Thomson D, Allin B, Long AM, et al. Laparoscopic assistance for primary transanal pull-through in Hirschsprung's disease: a systematic review and meta-analysis. BMJ Open. 2015;5:e006063.
33 Muller-Lissner SA, Kamm MA, Scarpignato C, et al. Myths and misconceptions about chronic constipation. Am J Gastroenterol. 2005;100:232–42.
34 Rao SS, Welcher KD, Leistikow JS. Obstructive defecation: a failure of rectoanal coordination. Am J Gastroenterol. 1998;93:1042–50.
35 Rao SS, Tuteja AK, Vellema T, et al. Dyssynergic defecation: demographics, symptoms, stool patterns, and quality of life. J Clin Gastroenterol. 2004;38:680–5.
36 Hyman PE. Defecation disorders after surgery for Hirschsprung's disease. J Pediatr Gastroenterol Nutr. 2005;41 Suppl 1:S62-3.

CHAPTER 12

Summary

Hirschsprung's disease (HD) is a congenital disease characterized by an absence of ganglion cells in the distal intestines, known as aganglionosis. The affected intestines are characterized by a constant increased tonus of the smooth bowel muscles, which blocks the passage of stool and results in persistent constipation. Aside from a constant increased tonus of bowel muscles, patients with HD also lack the rectoanal inhibitory reflex. In healthy bowels this reflex is responsible for the relaxation of the internal anal sphincter upon rectal distension and stimulation. Relaxation of the internal anal sphincter is vital for the smooth passage of stool. Consequently, the absence of this reflex in HD contributes to the constipation complaints experienced by HD patients.

HD is a relatively rare cause of constipation and occurs in an estimated 1 case per 5000 live births. In the majority of these patients, HD presents shortly after birth with a failure to pass meconium during the first 24 to 48 hours. The remaining group of HD patients, who often suffer from less severe disease, typically present with a history of chronic constipation and failure to thrive.

EARLY DIAGNOSIS

While clinical presentation can only suggest HD, the final diagnosis must be confirmed by the outcomes of rectal suction biopsy, anorectal manometry, and/or contrast enema. The rectal suction biopsy procedure entails extracting rectal tissue that is then sent to a pathology laboratory for histologic examination. The tissue is examined for the presence of intrinsic ganglion cells and the proliferation of extrinsic nerve fibers, whereby absence of ganglion cells combined with proliferation of nerve fibers is considered compatible with HD. Anorectal manometry can be used to examine anorectal physiology, including the presence of the rectoanal inhibitory reflex, which is absent in HD. The anorectal manometry procedure consists of inserting a catheter, equipped with pressure sensors and a small dilatation balloon at its tip, into the anal canal of the patient. As the rectal balloon is inflated, the pressure sensors at the level of the anal canal measure changes in anal sphincter pressure, which can then be used to test the functioning of the rectoanal inhibitory reflex. The contrast enema entails very slowly injecting a barium enema followed by an abdominal X-ray. A contrast enema carried out in an HD patient typically shows a contracted distal colon, a transition zone, and a distended colon in the caudal direction due to obstruction.

All three tests have been shown to have similar sensitivity and specificity, with the rectal suction biopsy being considered the gold standard. Despite this, however, recent reports have shown that rectal suction biopsy is also not an entirely satisfactory method, since its outcome may be affected by the patient's age. Additionally, while rectal suction

biopsy is generally considered safe and reliable, a small risk of complications, such as persistent rectal bleeding, remains. The primary aim of this thesis was therefore to improve the diagnostic process of determining HD, with the aim of increasing accuracy and reducing the number of invasive biopsy procedures.

In **Chapter 2**, we began with a retrospective analysis of all patients who had undergone one or more rectal suction biopsy between 1975 and 2011 in order to see if the patient's age indeed influenced the diagnostic accuracy of rectal suction biopsy. The results of this analysis show that the sensitivity (that is, proportion of positives that are correctly identified as such) of the rectal suction biopsy outcomes is significantly lower when the biopsies were obtained in patients younger than 39 days. In contrast, the specificity (that is, proportion of negatives that are correctly identified as such) of rectal suction biopsy outcomes was not influenced by age and remained high (95%) in all the age groups we investigated. These results corroborate our hypothesis that, in patients younger than 39 days, rectal suction biopsies are less reliable for the diagnosis of HD and should be analysed with utmost care.

In **Chapter 3**, we aimed to see whether anorectal manometry, used to test the functioning of the rectoanal inhibitory reflex, could be used to reduce the number of invasive rectal suction biopsy procedures needed to exclude HD. To test this hypothesis, we prospectively gathered the outcomes of 105 anorectal manometry results performed in patients suspected of having HD between 2010 and 2017. These results were compared to rectal suction biopsy results and final diagnoses. The results of this study showed that anorectal manometry scored equally well with respect to the diagnostic aspects of sensitivity and negative predictive value, whereas it scored significantly worse with respect to the aspects of specificity and positive predictive value. Nevertheless, we demonstrated that by correctly modifying the anorectal manometry protocol, one could improve performance in terms of these aspects. Importantly, there were no false negative anorectal manometry results obtained using anorectal manometry, which means it can be used to exclude HD with absolute certainty. In contrast, the false positive anorectal manometry results do mean that it continues to be necessary to perform a rectal suction biopsy in cases where no rectoanal inhibitory reflex was found through anorectal manometry.

In **Chapter 4**, we investigated whether anorectal manometry could also serve as a complement to rectal suction biopsy in the diagnosis of other causes of constipation in infants and children. For example, in the course of our studies on anorectal manometry,

we found patients in whom HD had been excluded by rectal suction biopsy but who still had an absence of the rectoanal inhibitory reflex during anorectal manometry. We hypothesized that in this group of patients, in whom HD had been excluded, absence or immaturity of the RAIR could be an explanation for their constipation complaints. Based on repeated measurements in nine patients, we concluded that immaturity of the rectoanal inhibitory reflex might indeed play a role in constipation in a subgroup of infants. Subsequently, the symptoms of constipation in these patients may improve as the rectoanal inhibitory reflex further matures.

In **Chapter 5**, we reported on two pediatric patients who suffered from solitary rectal ulcer syndrome, constipation, and chronic anemia, and who were finally diagnosed with HD at the age of 18 and 14 years, respectively. The aim of this report was to draw attention to pediatric patients presenting with solitary rectal ulcer syndrome as a possible sign of underlying but misdiagnosed HD. Early detection and proper diagnosis is vital for providing adequate treatment.

DEFECATION DISORDERS IN THE POPULATION

The second part of this thesis is dedicated to the development of our novel questionnaire on anorectal functioning: the Groningen Defecation and Fecal Continence (DeFeC) questionnaire. We chose to develop our own questionnaire, since all currently available questionnaires were either restrictive in content or focused solely on children or adults, which meant they were unsuitable for patient groups consisting of both. The DeFeC questionnaire, and its pediatric equivalent, will be used for the assessment of the long-term functional outcomes of HD, which was the second aim of this thesis.

In **Chapter 6**, we explained the contents of the DeFeC questionnaire and perform the initial validation experiments. The results show that the questionnaire was well understood, that its reproducibility was acceptable, and that the validity was good. This means that the DeFeC questionnaire is a practical tool in screening for defecation disorders. Importantly, since the questionnaire has both pediatric and adult versions, which are scored in comparable ways, it allows for the comparison of defecation disorders between pediatric and adult patients.

In **Chapter 7**, we reported the results of a cross-sectional study on the co-occurrence of constipation and fecal incontinence in the general population in the Netherlands using our newly developed questionnaire. We found that a relatively large proportion of the

Dutch population suffered from both constipation and fecal incontinence. The increased likelihood of fecal incontinence in constipated respondents lead us to conclude that constipation could be considered a causative factor of fecal incontinence. Importantly, the data obtained in this study can be used as normative data for future studies in patient populations, such as our own study on the long-term outcomes of HD.

LONG-TERM OUTCOMES

Following a brief digression on the development of our own questionnaire, we continued with the second aim of this thesis, namely to perform long-term follow-up studies of HD patients to assess their functional outcomes and quality of life.

Following the diagnosis of HD, patients are usually treated by performing a surgical reconstruction. Reconstruction consists of removing the majority of the aganglionic intestines in order to restore bowel functionality. Despite the best surgical efforts, studies often emphasize that HD is an incurable disease. This is illustrated by various reports noting that after surgical reconstruction, the majority of patients continue to suffer from defecation disorders, such as constipation and fecal incontinence. To date, it is not clear why some patients experience more difficulties than others. What is clear is that these disorders may have far-reaching consequences, because both constipation and fecal incontinence are known to negatively influence the quality of life. With this in mind, we set out to assess the long-term outcomes of HD with regard to both functional outcomes and quality of life. By doing so, we hoped to identify factors that cause some patients to experience more difficulties than others.

In **Chapter 8**, we presented the results of our nationwide, cross-sectional study on the long-term outcomes of HD. The collaboration of all six pediatric surgery centers resulted in a study population of 346 patients, all of whom completed questionnaires on anorectal functioning and quality of life. The main finding of this study was that, although improving with age, the symptoms of constipation and soiling persisted in a substantial group of adult HD patients. Additionally, we found that patients who underwent a second, redo pull-through procedure suffered from fecal incontinence more often. Although the influence of poor functional outcomes on quality of life in adult patients was limited, the persistence of defecation problems is an indication that continuous care may be recommended in a select group of adult patients.

In **Chapter 9**, we used a subgroup of patients from the nationwide study to perform a matched comparison of 52 patients treated by the Duhamel procedure and 52 patients

treated by the transanal endorectal pull-through (TERPT) procedure. The differences in functional outcomes following the Duhamel and TERPT procedures, if any, are small. Following the Duhamel procedure, patients used laxatives more often, although we showed that this may be negated by performing a laparoscopic Duhamel procedure, following which the usage of laxatives was significantly lower. Finally, our results showed that patients who underwent a completely transanal TERPT procedure had significantly higher prevalences of urge incontinence for both feces and urine, compared to patients who underwent a laparoscopic TERPT procedure.

In **Chapter 10**, we described a case series of post-operative HD patients with severe persistent constipation. Following defecometry, a test used to simulate the act of rectal evacuation, we diagnosed ten post-operative HD patients with dyssynergic defecation. Dyssynergic defecation is a disorder characterized by a paradoxical involuntary contraction of the external anal sphincter and/or puborectal muscle, which leads to a functional neuromuscular obstruction. Based on these ten cases, we believe it is important to consider the diagnosis of dyssynergic defecation when dealing with severe constipation in post-operative HD patients, especially since there are viable treatment options available that may prevent irreversible long-term complications, such as significant enlargement of the rectum and, eventually, overflow incontinence.

The main conclusions of this thesis are:

- Rectal suction biopsies obtained from infants less than 39 days old have a significantly lower sensitivity in terms of diagnosing Hirschsprung's disease, often lead to inconclusive outcomes, and often have to be repeated (*Chapter 2*)
- Anorectal manometry can be used to reduce the number of rectal suction biopsies needed to exclude Hirschsprung's disease (*Chapter 3*)
- Immaturity of the rectoanal inhibitory reflex may play a role in constipation in a select group of infants (*Chapter 4*)
- Solitary rectal ulcer syndrome should be considered as a possible presenting symptom for long-standing and unrecognized Hirschsprung's disease (*Chapter 5*)
- Functional outcomes improve with age, but symptoms of constipation and soiling persist in a substantial group of adult Hirschsprung's disease patients (*Chapter 8*)
- The differences in the functional outcomes of the Duhamel and transanal endorectal pull-through procedures are small, and the outcomes of both procedures can be further improved by using laparoscopy (*Chapter 9*)
- It is important to consider dyssynergic defecation when dealing with severe persistent constipation in postoperative Hirschsprung's disease patients (*Chapter 10*)

CHAPTER 13

Samenvatting

(Dutch summary)

De ziekte van Hirschsprung (ZvH) is een aangeboren aandoening van de darmen die zich vaak beperkt tot het laatste deel van de dikke darm. De ziekte wordt gekarakteriseerd door een afwezigheid van ganglioncellen (specifieke zenuwcellen van het spijsverteringsstelsel), ook wel aganglionose genoemd. Door de afwezigheid van deze zenuwcellen is de spierspanning van de aangedane darmen continue verhoogd en kunnen de darmen niet ontspannen, waardoor ze erg nauw en moeilijk doorgankelijk voor ontlasting zijn. Naast deze verhoogde spierspanning van de darmen missen patiënten met de ZvH ook de rectoanale inhibitiereflex. In gezonde darmen is deze reflex verantwoordelijk voor het ontspannen van de inwendige anale kringspier nadat de darmwand van de endeldarm geprikkeld wordt door ontlasting. Het functioneren van deze reflex is van vitaal belang voor een goede passage van ontlasting door de kringspier. Zowel de verhoogde spierspanning van de darmen als de afwezigheid van de rectoanale inhibitiereflex draagt bij patiënten met de ZvH bij aan hun obstipatieklachten.

De ZvH is een relatief zeldzame oorzaak voor obstipatie en komt in ongeveer 1 op de 5000 levendgeborene voor. In de meerderheid van de patiënten presenteert de ziekte zich vlak na de geboorte met het vertraagd passeren van de meconium (de eerste ontlasting van een pasgeborene), braken en een bolle buik. Patiënten bij wie de ziekte niet direct na de geboorte wordt vastgesteld lopen vaak lang rond met hardnekkige obstipatie en een afgenomen ontwikkeling.

VROEGE DIAGNOSE

Hoewel de klinische presentatie de diagnose ZvH kan doen vermoeden, moet de definitieve diagnose worden gesteld op basis van de uitslagen van rectumzuigbiopten, anorectale manometrie of coloninloopfoto. De rectumzuigbiopten bestaan uit het wegnemen van kleine stukjes weefsel van de endeldarm, die dan microscopisch onderzocht kunnen worden. Het weefsel wordt onderzocht op de aanwezigheid van ganglioncellen en proliferatie van zenuwbundels, waarbij een afwezigheid van ganglioncellen met toegenomen zenuwbundelproliferatie past bij de ZvH. Anorectale manometrie kan gebruikt worden om de fysiologie van het anorectum te onderzoeken, inclusief het functioneren van de rectoanale inhibitiereflex die afwezig is bij de ZvH. De procedure bestaat uit het inbrengen van een katheter, uitgerust met druksensoren en een kleine ballon aan het uiteinde, in het anale kanaal van de patiënt. Na het opblazen van de ballon en het stimuleren van de darmwand van de endeldarm kan vervolgens de spierspanning van de anale kringspier gemeten worden, wat uiteindelijk gebruikt kan worden om de rectoanale inhibitiereflex te testen. De coloninloopfoto bestaat uit het langzaam in laten lopen van bariumcontrast in de endeldarm om vervolgens een

röntgenfoto te maken. Een foto bij patiënten met de ZvH laat daarbij meestal een zeer nauw uiteinde van de dikke darm zien, met daarboven sterk uitgezette darmen door de obstructie in het laatste deel.

Alle drie de testen hebben ongeveer dezelfde nauwkeurigheid voor het stellen of uitsluiten van de diagnose van de ZvH, waarbij de rectumzuigbiopten als meest betrouwbaar worden beschouwd (ook wel de gouden standaard genoemd). Desondanks zijn er ook publicaties die suggereren dat de betrouwbaarheid van rectumzuigbiopten mogelijk beïnvloed wordt door de leeftijd van de patiënt, met daarbij een kans op gemiste of foutieve diagnoses. Daarnaast bestaat er bij het afnemen van weefsel tijdens de zuigbioptprocedure een kleine kans op complicaties, zoals een nabloeding of een perforatie van de darmwand. Het eerste doel van dit proefschrift was dan ook om het diagnostische traject bij de ZvH te verbeteren, met als voornaamste doel de betrouwbaarheid te verbeteren en het aantal invasieve zuigbioptprocedures te verminderen.

In **Hoofdstuk 2** zijn we gestart met een retrospectieve analyse van alle patiënten die rectumzuigbiopten hebben ondergaan tussen 1975 en 2011, om uiteindelijk te onderzoeken of de leeftijd van de patiënt ten tijde van het onderzoek invloed heeft gehad op de diagnostische betrouwbaarheid. De resultaten laten zien dat de sensitiviteit (het percentage patiënten met de ZvH dat een afwijkende bioptuitslag had) van rectumzuigbiopten significant lager is wanneer de biopten afgenomen worden bij patiënten jonger dan 39 dagen oud vergeleken met oudere patiënten. Daarentegen wordt de specificiteit (het percentage patiënten zonder ZvH dat een normale bioptuitslag had) van rectumzuigbiopten niet beïnvloed door de leeftijd van de patiënt en was die hoog (95%) in alle geteste leeftijdsgroepen. Deze resultaten ondersteunen onze hypothese dat, in patiënten jonger dan 39 dagen, rectumzuigbiopten minder betrouwbaar zijn voor het stellen van de diagnose ZvH en dat biopten op deze leeftijd bijzonder voorzichtig geïnterpreteerd moeten worden.

In **Hoofdstuk 3** hebben we gekeken of anorectale manometrie gebruikt kan worden voor het verminderen van het aantal invasieve rectumzuigbiopten dat nodig is in de diagnose van de ZvH, om zo de kans op complicaties te verminderen. Om onze hypothese te testen hebben we prospectief de uitkomsten van 105 anorectale manometriemetingen verzameld. Deze metingen zijn afgenomen bij patiënten verdacht van de ZvH in de periode van 2010 tot en met 2017. Deze resultaten hebben we vervolgens vergeleken met de uitkomsten van rectumzuigbiopten en met de uiteindelijke diagnoses. De resultaten van deze studie laten zien dat anorectale manometrie gelijk scoorde met betrekking

tot diagnostische aspecten zoals sensitiviteit en negatief voorspellende waarde, waarbij het minder scoorde met betrekking tot specificiteit en positief voorspellende waarde. Desondanks hebben we aangetoond dat aanpassingen in het anorectale manometrieprotocol ook deze laatste aspecten kunnen verbeteren. Nog belangrijker is dat we geen fout-negatieve uitslag van anorectale manometrie hebben waargenomen, wat betekent dat manometrie gebruikt kan worden om de ZvH met absolute zekerheid uit te sluiten. Wel betekent het aantal fout-positieve uitslagen dat een positieve anorectale manometrieuitslag altijd opgevolgd moet worden door rectumzuigbiopten om de definitieve diagnose te stellen.

In **Hoofdstuk 4** hebben we onderzocht of anorectale manometrie ook gebruikt kan worden als aanvulling op rectumzuigbiopten in de diagnose van andere oorzaken voor obstipatie in pasgeborenen en kinderen. Zo hebben we bijvoorbeeld tijdens onze analyse van de anorectale manometrieresultaten meerdere patiënten gevonden bij wie de ZvH uitgesloten was middels rectumzuigbiopten, maar bij wie wel een afwezigheid van de rectoanale inhibitiereflex werd gezien. Hierbij veronderstellen we dat in deze groep van patiënten, bij wie de ZvH uitgesloten is, afwezigheid of immaturiteit van de rectoanale inhibitiereflex een oorzaak kan zijn voor de obstipatieklachten. Op basis van herhaalde anorectale manometriemetingen in acht patiënten hebben we kunnen concluderen dat immaturiteit van de rectoanale inhibitiereflex inderdaad een rol zou kunnen spelen bij obstipatieklachten in een selecte groep kinderen. Dat betekent ook deze obstipatieklachten kunnen verbeteren als de rectoanale inhibitiereflex verder ontwikkeld.

In **Hoofdstuk 5** beschrijven we twee patiënten die langdurig leden aan het solitair rectumulcus-syndroom (een zweer in de darmwand van de endeldarm), obstipatie en chronische bloedarmoede, en die uiteindelijke gediagnosticeerd werden met de ZvH op de leeftijden van 18 en 14 jaar oud. Het doel van deze casusbeschrijvingen is om aandacht te vragen voor patiënten die zich presenteren met het solitair rectumulcus-syndroom als symptoom van een onderliggende, niet-erkende ZvH. Vroege herkenning en de juiste diagnose zijn namelijk vitaal voor een adequate behandeling.

ONTLASTINGSPROBLEMEN IN DE BEVOLKING

Het tweede deel van dit proefschrift is gericht op de ontwikkeling van onze nieuwe vragenlijst naar het functioneren van het anorectum: de Groningen Defecatie en Fecale Continentie (DeFeC)-vragenlijst. We hebben gekozen om onze eigen vragenlijst te

ontwikkelen omdat alle beschikbare vragenlijsten beperkt zijn of zich enkel richten op kinderen of volwassen, en dus ongeschikt zijn voor patiëntgroepen van zowel kinderen als volwassenen. De DeFeC-vragenlijst, en de kinderversie, zullen worden gebruikt voor het analyseren van de lange termijn uitkomsten van patiënten met de ZvH, wat het tweede doel van dit proefschrift is.

In **Hoofdstuk 6** leggen we de inhoud van de DeFeC-vragenlijst uit en beschrijven de we eerste validatieonderzoeken. De resultaten laten zien dat de vragenlijst goed begrepen werd, de reproduceerbaarheid acceptabel was en dat de validiteit goed was (in andere woorden, de vragenlijst meet wat het zou moeten meten). Dit betekent dat de DeFeC vragenlijst een goed instrument is om naar ontlastingsproblemen te screenen. Belangrijk is dat er zowel een volwassen- als een kinderversie van de vragenlijst is, wat het mogelijk maakt om beide groepen te kunnen vergelijken.

In **Hoofdstuk 7** rapporteren we de resultaten van een cross-sectioneel onderzoek naar het gelijktijdig voorkomen van obstipatie en fecale incontinentie in de Nederlandse bevolking met onze nieuwe vragenlijst. Hierbij hebben we gevonden dat een relatief groot deel van de Nederlandse bevolking lijdt aan zowel obstipatie als fecale incontinentie. Mede de verhoogde waarschijnlijkheid op fecale incontinentie bij mensen met obstipatie doet ons geloven dat obstipatie een belangrijke rol kan spelen in het ontstaan van fecale incontinentie. Ook kan de data verkregen in deze studie gebruikt worden als referentiedata voor toekomstige studies met patiëntgroepen, zoals onze eigen studie naar de langetermijnuitkomsten bij patiënten met de ZvH, omdat daarbij vaak een vergelijking gemaakt moet worden met een controle groep.

LANGETERMIJNUITKOMSTEN

In het derde deel van dit proefschrift gaan we verder met het tweede doel van dit proefschrift, namelijk het uitvoeren van lange termijn vervolgonderzoeken bij patiënten met de ZvH om zo hun functionele uitkomsten en kwaliteit van leven te analyseren.

Na de diagnose van de ZvH ondergaat het merendeel van de patiënten een operatieve ingreep. Deze ingreep bestaat uit het verwijderen van het aangedane, aganglionaire stuk darm om zo weer een goede doorgankelijkheid te verkrijgen. Ondanks de beste chirurgische inspanningen laten veel studies zien dat de ZvH ook na de operatie klachten kan geven. Zo laten meerdere publicaties zien dat een deel van de patiënten ontlastingsproblemen, zoals obstipatie en fecale incontinentie, behoudt na de operatie. Het is tot op heden niet duidelijk waarom sommige patiënten meer klachten ervaren

dan anderen. Wel is duidelijk dat deze klachten vergaande gevolgen kunnen hebben, aangezien van obstipatie en fecale incontinentie beide bekend is dat deze negatieve invloed hebben op de kwaliteit van leven. Met deze gedachte hebben we gepoogd om de langetermijnuitkomsten van patiënten met de ZvH goed in beeld te brengen, met daarbij oog op zowel de functionele uitkomsten als ook de kwaliteit van leven. Door dit onderzoek hopen we uiteindelijk factoren te vinden die kunnen verklaren waarom sommige patiënten meer klachten ervaren dan anderen.

In **Hoofdstuk 8** presenteren we de resultaten van ons landelijk, cross-sectioneel onderzoek naar de lange termijn uitkomsten van patiënten met de ZvH. De samenwerking van alle zes kinderchirurgische centra heeft tot een studiepopulatie van 346 patiënten geleid, die allen de vragenlijsten over het anorectaal functioneren en de kwaliteit van leven hebben voltooid. De belangrijkste bevinding van deze studie is dat hoewel ontlastingsproblemen afnemen naarmate patiënten ouder worden, een substantieel deel van de volwassen ZvH patiënten klachten van obstipatie en fecale incontinentie behoudt. Daarnaast hebben we ook gevonden dat patiënten die na hun eerste operatie nog een tweede operatie nodig hadden om tot een goed resultaat te komen op latere leeftijd vaker last hebben van fecale incontinentie. Hoewel de invloed van slechte functionele uitkomsten op de kwaliteit van leven in volwassenen beperkt was, lijken deze klachten toch een indicatie dat langdurige, continue zorg in een selecte groep patiënten nodig is.

In **Hoofdstuk 9** gebruiken we een subgroep van de patiënten uit de landelijke studie om een gepaarde vergelijking te maken tussen 52 patiënten die geopereerd zijn volgens de Duhamel-procedure en 52 patiënten die geopereerd zijn volgens de transanale endorectale doorhaal (transanal endorectal pull-through, TERPT)-procedure. De verschillen in functionele uitkomsten tussen beide procedures waren beperkt. Na de Duhamel-procedure gebruiken patiënten vaker laxantia (wat zou kunnen duiden op obstipatie), echter lieten onze resultaten ook zien dat dit verschil tenietgedaan kan worden door het uitvoeren van een laparoscopische Duhamel-procedure in plaats van een open procedure. Tot slot lieten onze resultaten zien dat patiënten wie een volledig transanale TERPT-procedure ondergingen een significant hogere prevalentie van urge-incontinentie voor zowel ontlasting als urine hadden vergeleken met patiënten die een laparoscopische TERPT-procedure ondergingen.

In **Hoofdstuk 10** beschrijven we een serie postoperatieve ZvH-patiënten met ernstige obstipatie. Na de defecometrietest, een onderzoek dat het proces van defecatie simuleert, werden alle tien patiënten gediagnosticeerd met dyssynerge defecatie.

Dyssynerge defecatie is een aandoening die gekarakteriseerd wordt door een paradoxale, onvrijwillige contractie van de uitwendige anale kringspier en de musculus puborectalis tijdens de defecatie waardoor er een functionele obstructie ontstaat ter hoogte van de anus (in plaats van de bekkenbodem te ontspannen tijdens het ontlasten spannen deze patiënten juist alles aan). Op basis van deze tien casussen denken wij dat het belangrijk is om aan de diagnose dyssynerge defecatie te denken bij postoperatieve patiënten met de ZvH die last hebben van ernstige obstipatie. Dit is met name belangrijk omdat er voor dyssynerge defecatie goede behandelingsmogelijkheden zijn die onomkeerbare langetermijncomplicaties, zoals decompensatie van de endeldarm en fecale incontinentie, kunnen voorkomen.

De voornaamste conclusies van dit proefschrift zijn:

- Rectumzuigbiopten verkregen bij patiënten jonger dan 39 dagen oud hebben een significant lagere sensitiviteit voor het diagnosticeren van de ziekte van Hirschsprung, geven vaak inconclusieve uitkomsten en moeten vaak herhaald worden (*Hoofdstuk 2*)
- Anorectale manometrie kan gebruikt worden om het aantal invasieve rectumzuigbiopten dat nodig is in het diagnosticeren van de ziekte van Hirschsprung te verminderen (*Hoofdstuk 3*)
- Immaturiteit van de rectoanale inhibitiereflex kan een rol spelen in obstipatieklachten bij een selecte groep van kinderen (*Hoofdstuk 4*)
- Het solitair rectumulcus-syndroom zou beschouwd moeten worden als een mogelijk presenterend symptoom van een langdurig bestaande, niet-erkende ziekte van Hirschsprung (*Hoofdstuk 5*)
- Functionele uitkomsten verbeteren met ouder worden, maar symptomen van obstipatie en fecale incontinentie persisteren in een substantieel deel van de volwassen ziekte van Hirschsprung patiënten (*Hoofdstuk 8*)
- De verschillen in functionele uitkomsten tussen de Duhamel- en transanale endorectale doorhaal-procedures zijn beperkt, en de uitkomsten van beide procedures kunnen verder verbeterd worden door het gebruik van laparoscopie (*Hoofdstuk 9*)
- Het is belangrijk om aan dyssynerge defecatie te denken bij het behandelen van ernstige obstipatie in postoperatieve patiënten met de ziekte van Hirschsprung (*Hoofdstuk 10*)

APPENDICES

The Groningen DeFeC questionnaire, abbreviations, dankwoord, about the author, list of publications

THE GRONINGEN DEFEC QUESTIONNAIRE

Instructions

1. Answer the questions by ticking the box next to your answer. Please tick just one answer to each question (unless you are invited to give more than one answer).
2. Although some of the questions may seem very similar, each one gives us important information. Some of the questions might relate to problems you do not have, but we want to know this too. Please answer every question (unless you are specifically told to proceed to another question).
3. There are no right or wrong answers. If you are unsure about how to answer a question, try to choose the answer that comes closest to your situation.
4. If you have any comments about the questionnaire, or if there is anything else you would like to say but which has not been covered by the questions, you can add your own comments at the end of the questionnaire.
5. Your answers will be treated in the strictest confidence.

Personal details

Surname _____

First name _____

Date of birth _____

Height (cm) _____

Weight (kg) _____

0.1 What is your gender?

☐ Male
☐ Female

0.2 What is your age in years?

_____

0.3 In which province do you live?

☐	Drenthe	☐	Noord-Brabant
☐	Flevoland	☐	Noord-Holland
☐	Friesland	☐	Overijssel
☐	Gelderland	☐	Utrecht
☐	Groningen	☐	Zeeland
☐	Limburg	☐	Zuid-Holland

0.4 How big is the town or village in which you live?

- ☐ I live in a village
- ☐ I live in a small town with fewer than 50,000 inhabitants
- ☐ I live in a medium-sized town with 50,000 to 100,000 inhabitants
- ☐ I live in a large town with more than 100,000 inhabitants

0.5 What is your highest level of education?

- ☐ Primary school education
- ☐ Level 1 or 2 BTEC or equivalent vocational qualification
- ☐ GCSEs with fewer than 5 grade A*-C or equivalent
- ☐ Level 3 or 4 BTEC or equivalent vocational qualification / apprenticeship
- ☐ 5+ GCSEs grade A*-C or equivalent
- ☐ 3+ A-Levels or equivalent
- ☐ Level 5 BTEC or equivalent vocational qualification / Foundation Degree
- ☐ University education
- ☐ Other, namely: _____

0.6 What is/was your job or profession?

_____

0.7 Are you still working?

- ☐ Yes, I work _____ hours per week
- ☐ No, I am no longer in paid employment, because:
- ☐ I spend my time doing housework and/or looking after the children
- ☐ I am retired or have taken early retirement
- ☐ I am at school, college or university
- ☐ I do not have a paid job due to problems with my bowels and/or pelvic floor
- ☐ I do not have a paid job due to other health problems
- ☐ I do not have a paid job for other reasons (e.g. I cannot find one, I do voluntary work, etc.)

0.8 In general, how would you describe your health in relation to the ability to hold and pass stools?

- ☐ Very good
- ☐ Good
- ☐ Reasonable
- ☐ Poor
- ☐ Very poor

Category 1: Defecation pattern

The following questions refer to your defecation pattern over the past six months.

1.1 On average, how often do you empty your bowels? (**Only tick one box**)

- ☐ Less than once a month
- ☐ Less than once a week
- ☐ Once a week
- ☐ Twice a week
- ☐ Once every two days
- ☐ Once or twice a day
- ☐ Three to five times a day
- ☐ More than five times a day

1.2 In general, what did your faeces look like (which type do you have most often)? (**Only tick one box**)

☐  Separate hard lumps (hard to pass)

☐  Sausage-shaped but lumpy

☐  Like a sausage but with cracks on its surface

☐  Like a sausage or snake, smooth and soft

☐  Soft blobs with clear-cut edges (passed easily)

☐  Fluffy pieces with ragged edges, a mushy stool

☐  Watery, no solid pieces (enterily liquid)

Category 2: Constipation

The following questions are about the difficulty you have had emptying your bowels over the past six months.

2.1 Did you have difficulty emptying your bowels (e.g. because of hard stools, not being able to pass all your stools or having to strain hard)?

- ☐ Yes
- ☐ No

2.1.1 If so, how long have you had this problem?

- ☐ 0-1 year
- ☐ 1 to 5 years
- ☐ 5 to 10 years
- ☐ 10 to 20 years
- ☐ Longer than 20 years

2.2 How often did you have to strain hard to empty your bowels?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Every day

2.3 On average, how long did you have to strain while emptying your bowels?

- ☐ Less than 5 minutes
- ☐ 5 to 10 minutes
- ☐ 10 to 20 minutes
- ☐ 20 to 30 minutes
- ☐ Longer than 30 minutes

2.4 How often did you have trouble passing stools because it felt as if there was a blockage?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Every day

2.5 How often did it feel as if you had not completely emptied your bowels after passing stools?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Every day

2.6 How often did you manage not to pass stools after feeling the urge to empty your bowels?

- ☐ I always manage
- ☐ One to three times a day
- ☐ Four to six times a day
- ☐ Seven to nine times a day
- ☐ More than nine times a day

2.7 How often did you have to return to the toilet within one hour of emptying your bowels to empty them again?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Every day

2.8 How often did you have pain in your anus while emptying your bowels?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Every day

2.9 Have you suffered from abdominal bloating?

- ☐ Yes
- ☐ No

2.9.1 If so, to what extent? (You may tick more than one answer)

- ☐ I only felt it myself
- ☐ Other people could also see it
- ☐ It made me lose my appetite or feel sick
- ☐ It made me vomit

2.10 How often did you have abdominal pain or cramps?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Every day

If you did not experience abdominal pain or cramps during the past six months, please proceed to question 3.1.

2.10.1 If you did experience abdominal pain or cramps, was this only during your menstrual period?

- ☐ No
- ☐ Yes
- ☐ Not applicable because I am post-menopausal
- ☐ Not applicable because I am a man

2.10.2 If you did experience abdominal pain or cramps, did they disappear or recede after you had emptied your bowels?

- ☐ Never or rarely
- ☐ Sometimes
- ☐ Often
- ☐ Usually
- ☐ Always

2.10.3 Do you have go to the toilet to empty your bowels more or less frequently since the abdominal pain or cramps started?

- ☐ Yes, I go to the toilet more frequently than before
- ☐ Yes, I go to the toilet less frequently than before
- ☐ No, I go to the toilet just as often as before

2.10.4 Has the consistency of your stools changed since the abdominal pain or cramps started? (Have they become harder or softer, for example)

- ☐ Yes, my stools are harder
- ☐ Yes, my stools are softer
- ☐ No, the consistency has not changed

Category 3: Constipation-related questions

The following questions relate to your diet and any remedies you may have used to help you empty your bowels during the past six months.

3.1 Do you drink at least 1.5 litres of fluids a day (10 x 150ml-cups/glasses)?

- ☐ Yes
- ☐ No

3.2 Do you eat at least 2 pieces of fruit a day?

- ☐ Yes
- ☐ No

3.3 Do you eat at least 3 tablespoons of vegetables a day?

- ☐ Yes
- ☐ No

3.4 Do you eat at least 3 slices of brown or wholemeal bread a day?

- ☐ Yes
- ☐ No

3.5 How often do you take laxatives to soften your stools/make it easier to empty your bowels?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ Several times a day

3.5.1 If you take laxatives, which one do you take and how much?

1. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
   Or per week: _____

2. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
   Or per week: _____

3. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
   Or per week: _____

3.6 Do you eat a special diet or foods to soften your stools?

- ☐ Yes, I eat /drink: _____
- ☐ No

3.7 Do you use an enema (= injecting a small amount of a medicine into the anus) to help pass stools?

- ☐ Yes, medicine: _____ dosage: _____ ml/cc
- ☐ No

3.7.1 If so, how often?

- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ times a day

3.8 Do you irrigate your rectum with lukewarm water (via the anus or by means of an antegrade colonic enema) to help you empty your bowels?

- ☐ Yes, amount: _____ ml/cc, with (if applicable): _____
- ☐ No

3.8.1 If so, how often did you irrigate?

- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ Several times a day

3.9 Do you ever use your fingers or hands to help pass stools? (You may tick more than one answer)

- ☐ Yes, I press on my abdomen with my hands
- ☐ Yes, I use my finger to press between my buttocks, just in front the anus
- ☐ Yes, I use my finger to press between my buttocks, just behind the anus
- ☐ Yes, I use my fingers to remove stools from my anus
- ☐ Yes, but in another way, namely: _____
- ☐ No

3.9.1 If so, how often do you use your fingers or hands when passing stools?

- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Every day

3.10 If you had difficulty passing stools, have you ever talked to anyone about it? (You may tick more than one answer)

- ☐ Not applicable, I do not have difficulty passing stools
- ☐ Yes, with family or friends
- ☐ Yes, with my GP
- ☐ Yes, with a medical specialist
- ☐ Yes, with someone else, namely: _____
- ☐ No

Category 4: Faecal continence

The following questions are about the accidental passage of stools during the past six months.

4.1 How often did you accidentally pass small amounts of faeces? (i.e. stained/soiled your underpants)

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ Several times a day

4.1.1 If you accidentally passed small amounts of faeces, when did this happen? (You may tick more than one answer)

- ☐ When I had diarrhoea
- ☐ When I was desperate for the toilet
- ☐ During physical activity/exertion
- ☐ For no clear reason

4.2 How often did you accidentally pass large amounts of solid faeces without having felt an urge (i.e. without feeling the need for the toilet)?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ Several times a day

4.3 How often did you feel a strong urge to empty your bowels but were unable to reach the toilet in time?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ Several times a day

4.4 How often did you accidentally pass watery stools (diarrhoea)?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ Several times a day

4.5 How often did you accidentally pass wind?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ Several times a day

If you have not accidentally passed liquid or solid stools during the past six months, please proceed to question 5.1.

4.6 If you have accidentally passed faeces, how much was this on average?

- ☐ A tiny amount, about the size of a coin
- ☐ Enough to make me change my underpants
- ☐ Enough to make me change my underpants and trousers

4.7 If you accidentally passed faeces, when did this happen?

- ☐ Only while I was awake
- ☐ Only while I was asleep
- ☐ While I was awake and while I was asleep

4.8 How often did you use panty liners or incontinence pads to help when you accidentally passed faeces?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ Several times a day

4.9 How often did you rearrange your daily programme because of accidentally passing faeces (e.g. stayed at home, cancelled an appointment, changed your diet)?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ Several times a day

4.10 Have you ever accidentally passed faeces shortly after emptying your bowels on the toilet?

- ☐ Yes
- ☐ No

4.11 Do you use an anti-diarrhoea medicine to solidify your stools?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day
- ☐ Several times a day

4.11.1 If you use an anti-diarrhoea medicine, which one do you use and how much?

1. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
   Or per week: _____

2. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
   Or per week: _____

3. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
   Or per week: _____

4.12 Do you eat a diet or eat particular foods to control accidental passage of stools?

- ☐ Yes, I eat/drink: _____
- ☐ No

4.13 Do you irrigate your bowels with lukewarm water to control accidental passage of stools?

- ☐ Yes, amount: _____ ml/cc, with (if applicable): _____
- ☐ No

4.14 Have you ever talked to anyone about losing control of your bowels? (You may tick more than one answer)

- ☐ Yes, with family or friends
- ☐ Yes, with my GP
- ☐ Yes, with a medical specialist
- ☐ Yes, with someone else, namely: _____

Category 5: Urge

The following questions are about your urge to go the toilet over the past six months.

5.1 Did you feel the urge to empty your bowels before you went to the toilet?

- ☐ Yes
- ☐ Sometimes
- ☐ No

5.2 On average, how long were you able to control your bowels once you had felt the urge to go to the toilet?

- ☐ I was unable to control my bowels
- ☐ One minute or less (I always had to go to the toilet immediately)
- ☐ Five minutes at the most
- ☐ Fifteen minutes at the most
- ☐ I never had to hurry

5.3 How often did you have to hurry to get to the toilet in time, to prevent yourself accidentally passing stools?

- ☐ Never
- ☐ Less than once a month
- ☐ Several times a month
- ☐ Several times a week
- ☐ Once a day

5.4 When you felt the urge to go to the toilet, could you tell the difference between flatulence, diarrhoea and solid/hard stools?

- ☐ Yes
- ☐ With difficulty
- ☐ No

Category 6: Urinary incontinence

The following questions concern bladder control over the past six months.

6.1 On average, how often did you urinate?

- ☐ Less than three times a day
- ☐ Three to seven times a day
- ☐ More than seven times a day

6.2 When you urinated, were you able to empty your bladder in one go?

- ☐ Yes, the urine stream was never interrupted
- ☐ No, the urine sometimes came in bursts (stopped and started)
- ☐ No, the urine always came in bursts (stopped and started)

6.3 When you urinated, did you have to strain?

- ☐ Yes, I always had to strain while urinating
- ☐ Yes, I sometimes had to strain while urinating
- ☐ No, I never had to strain while urinating

6.4 How often did you accidentally lose urine?

- ☐ Never
- ☐ About once a week or less
- ☐ Two to three times a week
- ☐ About once a day
- ☐ Several times a day
- ☐ Continuously

6.5 How much urine did you lose on average (irrespective of whether you used pads)?

- ☐ None
- ☐ A bit (a few drops)
- ☐ Quite a lot (wet underpants)
- ☐ A lot (visible wet patches)

6.6 When did you accidentally lose urine? (You may tick more than one answer)

- ☐ Never, I did not lose any urine
- ☐ Before I could reach the toilet
- ☐ Whenever I sneezed or coughed
- ☐ While I was asleep
- ☐ During physical activity/exertion
- ☐ When I got dressed again after urinating
- ☐ For no clear reason
- ☐ Continuously

6.7 How often did you need to go to the toilet during the night?

- ☐ Never/rarely
- ☐ Once or twice a week
- ☐ Three to six times a week
- ☐ Every night
- ☐ Several times a night

6.8 How often did you feel as if you had a bladder infection in the past 6 months?

- ☐ Never
- ☐ Once
- ☐ Several times

6.9 How often have you been treated for a bladder infection in the past 6 months?

- ☐ Never
- ☐ Once
- ☐ Several times

Category 7: Obstetric and gynaecological history

The following questions only apply to women. If you are a man, please proceed to question 8.1.

7.1 Have you ever been through childbirth (including caesarean section)?

- ☐ Yes
- ☐ No

7.1.1 If so, how many times?

_____

7.2 How many of these were natural (vaginal) deliveries?

_____

If you have never experienced a vaginal delivery, please proceed to question 7.7.

7.3 How long did you have to push during your longest delivery?

- ☐ Less than one hour
- ☐ One to two hours
- ☐ Longer than two hours

7.4 Were obstetrical instruments used during any of these vaginal deliveries?

- ☐ Yes
- ☐ No

7.4.1 If so, which instruments were used? (You may tick more than one answer)

- ☐ Forceps
- ☐ A vacuum extractor
- ☐ Other, namely: _____

7.5 Did you need an incision in the perineum (episiotomy) or did you rupture during a vaginal delivery, to the extent that the pelvic floor muscles around your anus were affected?

- ☐ Yes
- ☐ No

7.5.1 If so, what happened? (You may tick more than one answer)

- ☐ I ruptured
- ☐ I had an incision in the perineum (episiotomy)
- ☐ Other, namely: _____

7.6 What was the weight of your **heaviest** baby?

_____ grams

7.7 Has your uterus been removed (a hysterectomy)?

- ☐ Yes, via the vagina (vaginal)
- ☐ Yes, via the abdomen (abdominal)
- ☐ No

7.8 When you are emptying your bowels, does it ever feel as if something is hanging out or descending through your vagina?

- ☐ Yes
- ☐ No

Category 8: Medical history

The following questions relate to conditions or operations that may affect your bowel control.

8.1 Have you ever undergone one of the following surgical procedures that may affect your bowel control? (You may tick more than one answer)

- ☐ No, I have never had an operation on my bowels, anus or prostate
- ☐ Removal of a section of bowel, after which the remaining sections were sutured together
- ☐ Operation on a fistula in the anal cleft close to the anus (perianal fistula)
- ☐ Operation on the anal sphincter
- ☐ Operation for haemorrhoids
- ☐ Operation on the prostate
- ☐ Other, namely: _____

Procedure to repair a hereditary condition, such as:

- ☐ Anal atresia or congenital anorectal malformation
- ☐ Hirschsprung's disease
- ☐ Sacrococcygeal teratoma

8.2 Do you have (or have you had) a stoma to remove faeces from your bowel?

- ☐ Yes, a colostomy
- ☐ Yes, an ileostomy
- ☐ No

8.3 Do you ever have blood and/or mucous in your stools?

- ☐ Yes
- ☐ No

8.4 Have you ever had an injury to your anus, apart from during childbirth or an operation?

- ☐ Yes, namely: _____
- ☐ No

8.5 Have you ever had, or are you still experiencing the after-effects of, one of the following medical conditions? (You may tick more than one answer)

- ☐ I have never had any of the conditions listed below
- ☐ Crohn's disease or colitis ulcerosa (inflammation of the colon)
- ☐ Irritable bowel syndrome
- ☐ Prolapse of the rectum
- ☐ Diabetes mellitus
- ☐ Cerebral haemorrhage or infarction (stroke)
- ☐ Another neurological conditions (e.g. paraplegia, multiple sclerosis)
- ☐ Slow transit constipation

Hereditary conditions such as:

- ☐ Anal atresia or congenital anorectal malformation
- ☐ Hirschsprung's disease
- ☐ Sacrococcygeal syndrome
- ☐ Spina bifida
- ☐ Other, namely: _____

8.6 Does one of the medical conditions you have ticked occur in your family?

- ☐ Yes
- ☐ No
- ☐ Not applicable

8.6.1 If so, which conditions occur in which members of your family?

Condition: _____ Relative: _____

Condition: _____ Relative: _____

Condition: _____ Relative: _____

Condition: _____ Relative: _____

8.7 Which medicines do you take at the moment (you do not need to mention the laxatives and anti-diarrhoea treatments mentioned previously)?

☐ I do not take any other medication.

☐ I take:

1. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
2. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
3. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
4. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
5. Medicine: _____ How often per day: _____ Dosage: ____ ml/g
6. Medicine: _____ How often per day: _____ Dosage: ____ ml/g

You have come to the end of the questionnaire.

Thank you very much for taking the time to answer these questions.

If there is anything else you would like to say, or if there is something you feel was not covered or not covered sufficiently by this questionnaire, please use the space below to leave your comments.

Digital version of the questionnaire (pdf)

ABBREVIATIONS

ACh	Acetylcholine
AChE	Acetylcholinesterase
ARM	Anorectal manometry
CI	Confidence interval
CGS	Continence grading scale
CSS	Constipation scoring sytem
DeFeC	Defecation and fecal continence (questionnaire)
EAS	External anal sphincter
ENS	Enteric nervous system
FI	Fecal incontinence
HD	Hirschsprung's disease
H&E	Hematoxylin and eosin
IAS	Internal anal sphincter
ICC	Intraclass correlation coefficient
NADH	Nicotinamide adenine dinucleotide
NO	Nitric oxide
OR	Odds ratio
QoL	Quality of life
RACR	Rectoanal contractile reflex
RAIR	Rectoanal inhibitory reflex
RSB	Rectal suction biopsy
SRUS	Solitary rectal ulcer syndrome
TERPT	Transanal endorectal pull-through

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Rob Meinds

ABOUT THE AUTHOR

Rob Jelle Meinds was born on July 15th, 1992 in Stadskanaal, the Netherlands, where he grew up and attended primary and secondary education. Following his graduation in 2010 he started his studies in medicine at the University of Groningen. In 2013 he started his first scientific clerkship under the supervision of dr. Broens, which sparked his enthusiasm for research. His initial research on the subject of Hirschsprung's disease led to his first scientific publication and the possibility to successfully apply for the MD/PhD programme of the University of Groningen in 2014. This trajectory allows students to continue their research and to obtain a PhD degree in an additional two years next to their regular study. In the subsequent years he worked on the research which is presented in this thesis. Following the completion of his last scientific work and final internships, Rob graduated from medical school in August 2018. Since September 2018 he has started his first job as a physician at the Department of Gastroenterology of the Medisch Spectrum Twente in Enschede. In his spare time he continues to enjoy cooking, travelling, and cycling.

LIST OF PUBLICATIONS

2019

Meinds RJ, van der Steeg AFW, Sloots CEJ, Witvliet MJ, de Blaauw I, van Gemert WG, Trzpis M, Broens PMA. Long-term functional outcomes and quality of life in patients with Hirschsprung's disease. Br J Surgery (In press).

2018

Meinds RJ, Trzpis M, Broens PMA. Anorectal manometry may reduce the number of rectal suction biopsy procedures needed to diagnose Hirschsprung's disease. J Pediatr Gastroenterol Nutr. 2018;67:322-7.

Meinds RJ, Timmerman MEW, van Meegdenburg MM, Trzpis M, Broens PMA. Reproducibility, feasibility, and validity of the Groningen Defecation and Fecal Continence questionnaires. Scand J Gastroenterol. 2018;53:790-6.

van Meegdenburg MM, Meinds RJ, Trzpis M, Broens PMA. Subtypes and symptoms of fecal incontinence in the Dutch population: a cross-sectional study. Int J Colorectal Dis. 2018;33:919-25.

2017

Meinds RJ, van Meegdenburg MM, Trzpis M, Broens PMA. On the prevalence of constipation and fecal incontinence, and their co-occurrence, in the Netherlands. Int J Colorectal Dis. 2017;32:475-83.

2016

Meinds RJ, van der Doef HPJ, Bodewes FAJA, Timmer A, Trzpis M, Broens PMA. Solitary rectal ulcer syndrome as a sign of unrecognized Hirschsprung's disease. J Pediatr. 2016;177:321-321e.

2015

Meinds RJ, Kuiper GA, Parry K, Timmer A, Groen H, Heineman E, Broens PMA. Infant's Age Influences the Accuracy of Rectal Suction Biopsies for Diagnosing of Hirschsprung's Disease. Clin Gastroenterol H. 2015;13:1801-7.

2014

Meinds RJ, Eggink MC, Heineman E, Broens PMA. Dyssynergic defecation may plan an important role in postoperative Hirschsprung's disease patients with severe persistent constipation: analysis of a case series. J Pediatr Surg. 2014;49:1488-92.