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

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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.

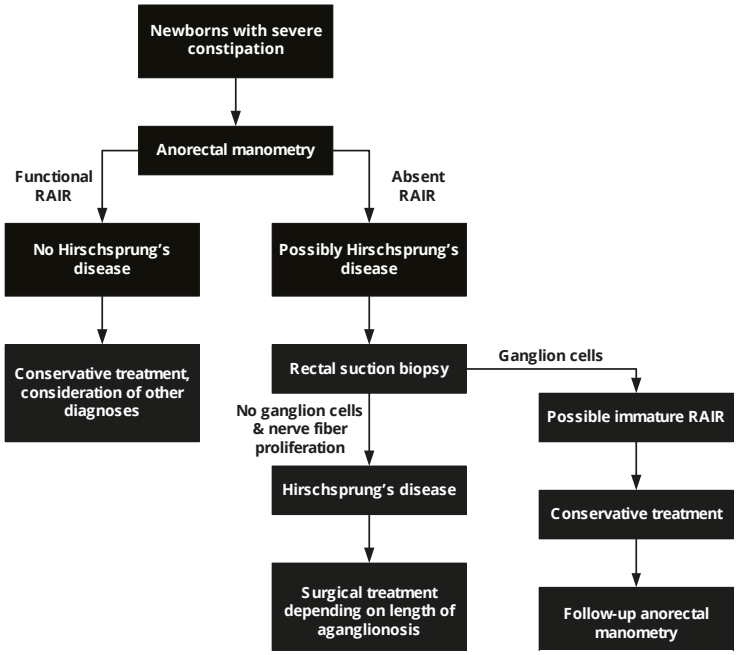

Figure 1

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.

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