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

Meinds, Rob Jelle

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*)