university of groningen

University Medical Center Groningen

University of Groningen

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

Meinds, Rob Jelle

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Meinds, R. J. (2019). *Hirschsprung's disease: early diagnosis and long-term outcomes*. [Thesis fully internal (DIV), University of Groningen]. Rijksuniversiteit Groningen.

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 19-03-2025

CHAPTER 4

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

Rob J. Meinds[1], M. Trzpis[2], Paul M.A. Broens[1,2]

1 Department of Surgery, Division of Pediatric Surgery, University Medical Center Groningen
2 Department of Surgery, Anorectal Physiology Laboratory, University Medical Center Groningen

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

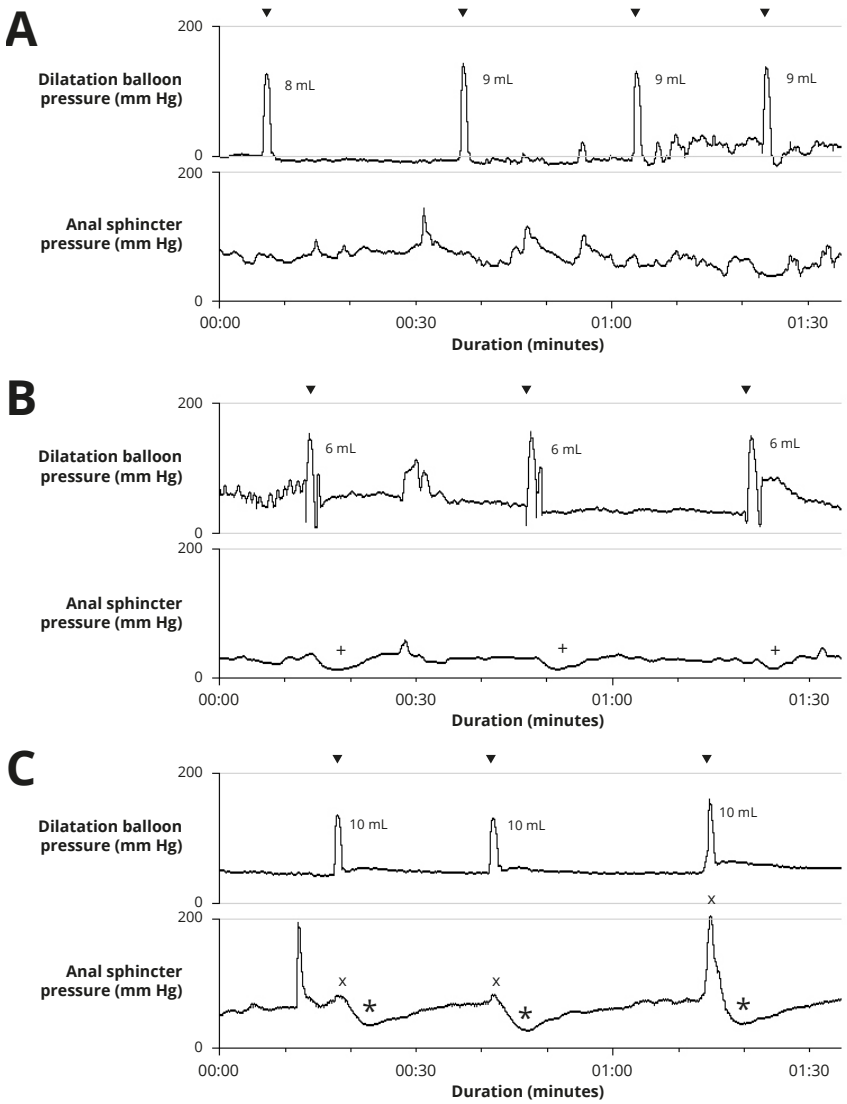

Figure 1

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

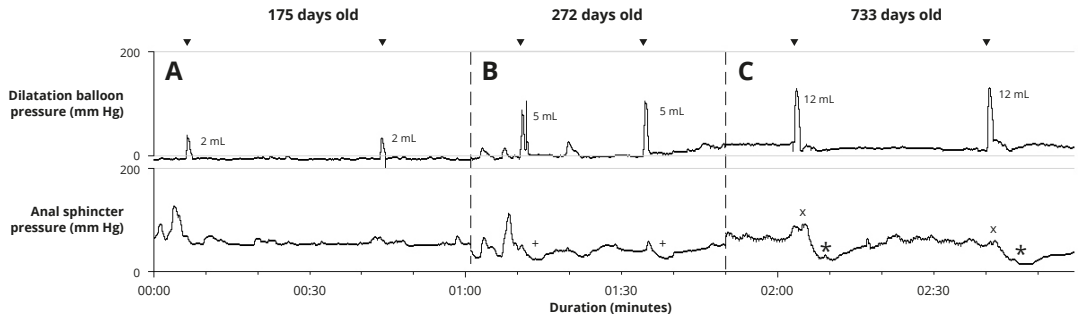

Figure 2

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.

ACKNOWLEDGEMENTS

The authors thank Mrs. O.J. Pras, Mrs. T. de Groot, Ms. S. Gerritsen, and Mrs. B. Brongers-Posthuma of the Anorectal Physiology Laboratory for their substantial assistance in performing the measurements. In addition, we would like to thank T. van Wulfften Palthe, PhD, for correcting the English manuscript.

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.