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

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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.

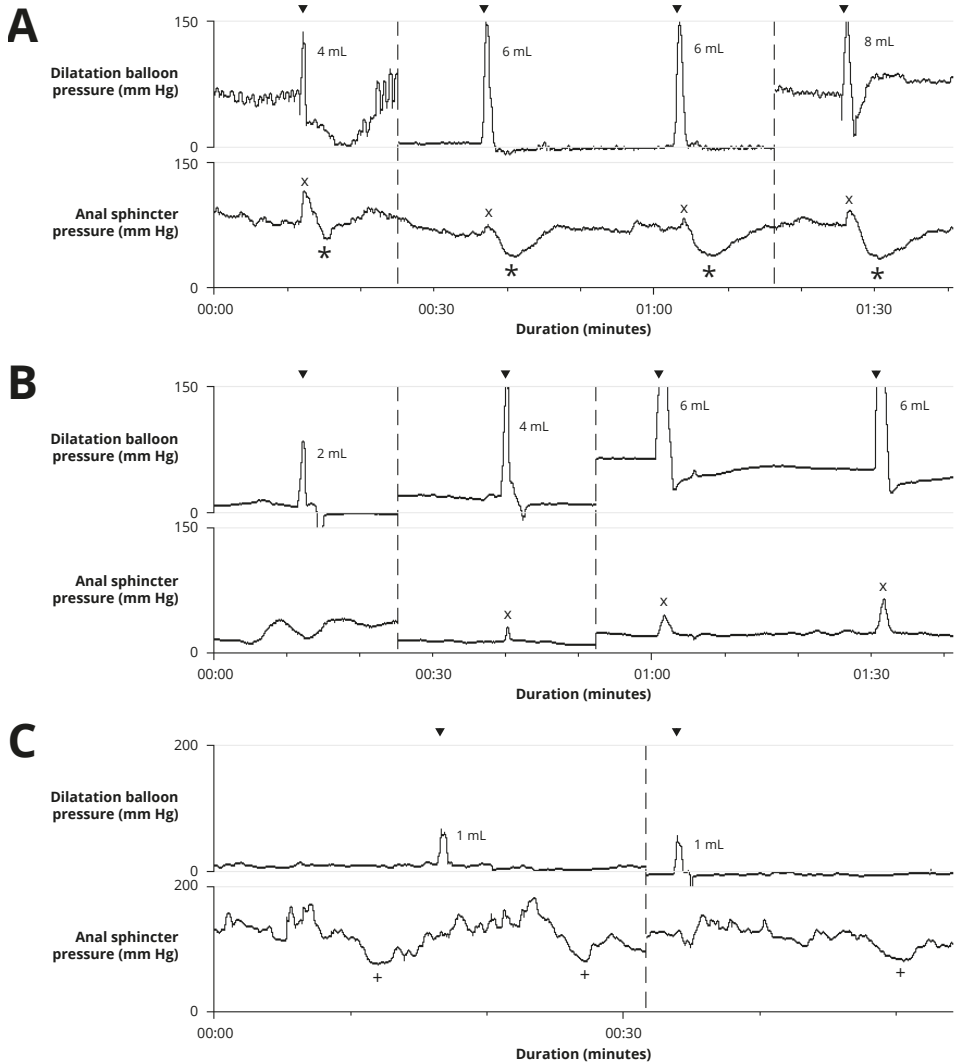


Figure 1

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.

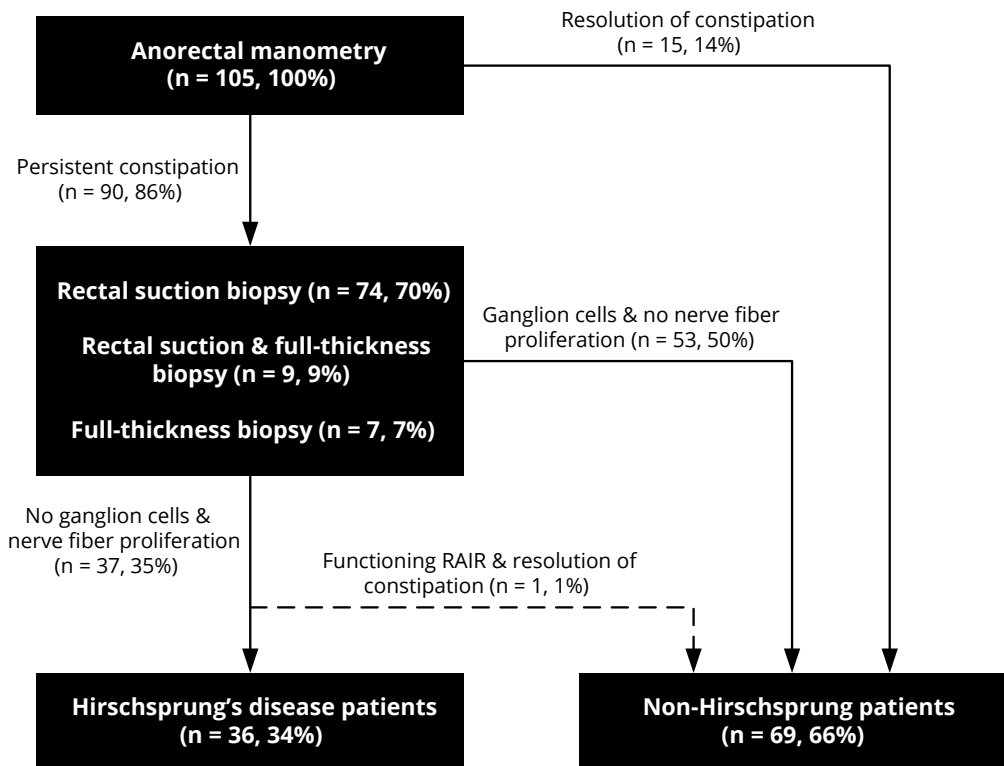


Figure 2

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. (%)	<i>P</i> 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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