



Research article

Exploring the value of rectal anal canal pressure measurement in the diagnosis of Hirschsprung's disease

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HIGHLIGHTS

- This prospective study was performed to explore the value of anorectal manometry (ARM) in the diagnosis of Hirschsprung's disease (HD) through age stratification.
- Although there have been similar studies, most of the studies included children who had not undergone rectal suction biopsy (RSB) examination due to the small sample size in the diagnosis of HD. In our study, the children we included all had ARM and RSB test results, and the RSB results had not been known before ARM. The research method of comparing the difference between the two examination results of the same individual has a higher degree of credibility.
- The results revealed that ARM has high sensitivity in HD children of all ages. However, in neonates, ARM has a high false positive rate in the diagnosis of HD.

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ABSTRACT

Background: The value of rectal anorectal manometry (ARM) in the diagnosis of Hirschsprung's disease (HD), especially in newborns, has been controversial. This study aims to further explore the value of ARM in the diagnosis of HD.

Methods: This study prospectively collected the rectal and anal canal pressure records of children with high suspicion of HD diagnosed by rectal suction biopsy (RSB) from the West China Hospital of Sichuan University from November 2019 to September 2021. With RSB results as the diagnostic gold standard, the value of ARM examination in the diagnosis of HD was explored through age stratification.

Results: Among 170 children, the sensitivity of ARM in diagnosing HD was 98%, the specificity was 65%, and the accuracy was 93%. The positive likelihood ratio was 2.83, and the negative likelihood ratio was 0.03. The positive result of ARM is more important to HD. The positive predictive value was 94%, the negative predictive value of the ARM negative result for HD was 85%, the kappa value was 0.680, and the Yuedeng index was 0.63. Through age stratification, it was found that the sensitivity of ARM for HD diagnosis in each age group was relatively close, but the neonatal specificity was only 33%, which was significantly lower than that of children of other age groups.

Conclusion: ARM has high sensitivity in HD children of all ages. In neonates, ARM has a high false positive rate in the diagnosis of HD.

1. Introduction

Hirschsprung's disease (HD) is a more common developmental malformation of the gastrointestinal tract. The distal colon and rectum lack ganglion cells, which leads to congenital intestinal malformations with spasmodic stenosis of the intestinal tract. It often leads to repeated abdominal distension and constipation after birth, which seriously affects the growth and development of the child. There are many perioperative complications of the disease. Severe enterocolitis can

endanger the life of the child and has a high mortality rate [1]. The clinical manifestations of HD are not typical, such as the most common presentation of delayed passage of meconium or abdominal distension in the neonatal period. HD usually needs to be differentiated from simple meconium constipation, neonatal peritonitis, neonatal enterocolitis, hypothyroidism, secondary Hirschsprung disease and Hirschsprung allied disease (HAD). Therefore the workload of HD screening is heavy. Currently, rectal suction biopsy (RSB) is the gold standard for diagnosing HD [2]. However, due to the uncertainty of the test results,

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17% of children still require repeated biopsy [3], and RSB is invasive and has the risk of complications [4]. Anorectal manometry (ARM) is a high-definition, feasible, noninvasive test with almost no risk. In healthy individuals, rectal balloon stimulation will cause rectoanal contractile reflex (RACR) and rectoanal inhibitory reflex (RAIR) [5]; however, in HD patients, there is no RAIR [6, 7, 8]. Therefore, failure to find RAIR during the ARM test may indicate HD, but scholars still believe that ARM has high false negatives and false positives, especially in neonates [9, 10, 11]. This study uses RSB as the diagnostic gold standard to explore the accuracy of ARM diagnosis and further clarify the role of ARM in HD screening and diagnosis.

2. Objects and methods

2.1. Research objects and methods

This study prospectively collected the rectal and anal canal pressure records of children with high suspicion of HD who were diagnosed by RSB at the Pediatric Surgery Department of West China Hospital of Sichuan University from November 2019 to September 2021. The RSB results were used as the diagnostic gold standard to explore the sensitivity, specificity, accuracy, positive and negative likelihood ratios, and positive and negative predictive values of the ARM test in the diagnosis of HD. Inclusion criteria: ① All children underwent RSB in the research institute in the hospital and completed ARM examinations in the hospital before RSB. ② All ARM examinations were completed by two nurses with 10 years or more of clinical experience in pediatric surgery, and the examinations were carried out in accordance with a unified standard process. Exclusion criteria: ① Patients with severe cardiovascular and cerebrovascular diseases, vital organ dysfunction, such as complicated bruising congenital heart disease, severe pneumonia, etc. ② The results of RSB in other hospitals were obtained before ARM. The hospital of the research institute routinely performed ARM on children with constipation, and the guardians of the children were informed and signed an informed consent form for the operation.

2.2. ARM implementation of standard procedures and methods

ARM was performed after the child was nil by mouth for at least 2 h. After bowel preparation and sedation where necessary, ARM was performed with the child in the supine position using a perfusion system (MMS Company, Netherlands, 4 channels of 4 mm diameter). The resting pressure of the anal canal was recorded before gas injection and whether there was RAIR elicitation and its threshold after gas injection. At least 3 or more RAIRS were recorded.

2.3. RSB inspection process and result judgment

Specimen collection was completed by pediatric general surgeons with more than 10 years of experience in pediatric surgery and surgery. Two levels of samples were taken, namely, 1 and 3 cm or 2 and 4 cm above the dentate line. This hospital mainly uses CR, Glut-1, S-100 and other immunohistochemical staining methods to carry out systematic screening and analysis of HD genes and positively expressed proteins. When the result cannot be judged, if insufficient material is suspected, another biopsy is recommended. If the family refuses, the judgment will be based on the pathological diagnosis of the child during the operation or combined with the clinical follow-up.

2.4. Data collation

Two people sorted out and verified the data. The value of the resting pressure of the anal canal was accurately recorded, and the rectal anal canal pressure test and whether the RSB results were consistent with the diagnosis of HD were sorted into binary variable data.

2.5. Sample size estimation

According to the method of estimating the sample content of the overall rate in the diagnostic test study, the "disease" group n_1 and the "disease free" group n_2 were calculated. $n_1 = \frac{Z_{\alpha}^2 Sen(1-Sen)}{6}$, $n_2 = \frac{Z_{\alpha}^2 Spe(1-Spe)}{6}$. Among them, set $\alpha = 0.05$, $Z_{\alpha} = 1.96$, consult foreign literature [12], set sensitivity (Sen) = 0.90, assume the sensitivity tolerance $\delta_{sen} = 0.05$, specificity (Spe) = 0.70, assume the specificity tolerance $\delta_{spe} = 0.1$, calculate $n_1 = 7$; $n_2 = 9$.

2.6. Statistical methods

SPSS 26.0 was used for data processing and statistical analysis; sensitivity, specificity, accuracy, positive and negative likelihood ratios, and positive and negative predictive values were used to evaluate the accuracy of the ARM test in the diagnosis of HD; and the value of ARM in the diagnosis of HD was further analyzed through age stratification. Normally distributed measurement data are represented by the mean \pm standard deviation ($\bar{x} \pm s$), nonnormally distributed measurement data are represented by the median (interquartile range) [M(IQR)], and count data are represented by the frequency and composition ratio. According to the data type, the paired t test or the rank sum test was selected to compare the difference in the resting pressure of the anal canal. A two-sided test was used, and the test level was $\alpha = 0.05$.

2.7. Ethical principles

This study was reviewed and approved by the Institute's Biomedical Ethics Committee in the hospital, and the ethics number is 2020 Examination (224).

3. Results

3.1. General information

This study included a total of 170 children, including 125 males (73.5%) and 45 females (26.5%). The median age was 16.76 (6.03, 40.17) months, the minimum age was 3 days, and the oldest age was 187.10 months. The specific results of ARM and RSB diagnosis are shown in Table 1.

2.2 The sensitivity of ARM in diagnosing HD in 170 children was 98%, specificity was 65%, accuracy was 93%, positive likelihood ratio was 2.83, negative likelihood ratio was 0.03, and the ARM positive result was positive for the final HD, the predictive value is 94%, the negative predictive value of the ARM negative result for the final HD is 85%, the kappa value is 0.680, and the Yuedeng index is 0.63. RSB was diagnosed as HD (-) mean resting pressure (20.04 \pm 15.19) mmHg and HD (+) mean

Table 1. Four-frame table for ARM diagnosis of HD in each age group.

Age groups	RSB		Total		
	HD (+)	HD (-)			
Newborn	ARM	HD (+)	7	4	11
		HD (-)	0	2	2
	Total		7	6	13
Infants 28 days old and less than 6 months old	ARM	HD (+)	23	2	25
		HD (-)	1	5	6
	Total		24	7	31
Over 6 months	ARM	HD (+)	111	3	114
		HD (-)	2	10	12
	Total		113	13	126
Total	ARM	HD (+)	141	9	150
		HD (-)	3	17	20
	Total		144	26	170

Table 2. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value of ARM in the diagnosis of HD in each age group.

Project	Age groups	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Negative predictive value (%)
ARM	Newborns	100	33	69	64	100
	Infants 28 days old and less than 6 months old	96	71	90	92	83
	Over 6 months	98	77	96	97	83

resting pressure (21.02 ± 14.19) mmHg, and the difference was not statistically significant ($t = -0.303$, $P = 0.762$).

2.3 Through further stratified analysis of age, it is found that the sensitivity and negative predictive value of newborns, infants 28 days old and less than 6 months old, and children over 6 months of HD diagnosis are relatively close, and the specificity and positive predictive value are higher. There are obvious differences. The four-cell table for the diagnosis of HD by ARM in each age group is shown in Table 1. The sensitivity, specificity, accuracy, and positive and negative predictive values of the diagnosis of each age group are shown in Table 2.

4. Discussion

Due to the lack of ganglion cells in the muscular layer and submucosal nerve plexus of the distal colon and rectum in children with HD, the anorectal sphincter does not exhibit RAIR due to rectal expansion, which causes severe constipation and affects the normal growth and development of children. It has caused much trouble to the families of sick children. With changes in dietary structure and living environment, constipation in children has become increasingly common [13]; therefore, higher requirements for the screening and diagnosis of HD have been put forward. At present, the most reliable diagnostic method for HD is RSB [2], but because the test is an invasive operation, it is not suitable as a preliminary screening method. After people have realized that RAIR is an important part of the normal bowel reflex, it is also an important sign reflecting the function of the internal sphincter. Using ARM to understand the presence or absence of sphincters has become an important technique for the diagnosis of HD without injury. However, the lack of a unified and standardized operation process and the greater dependence on the operator's own experience for inspection have led to large differences in the accuracy of the application of ARM in the diagnosis of HD at home and abroad [14, 15, 16, 17]. In this study, the pressure measurement of 144 children with HD found that the diagnosis rate of ARM for HD was as high as 98%, and the missed diagnosis rate was only 2%. This depends on the unified standardized operation procedure developed in this study, and the gas injection gradient of 5 ml greatly shortens the examination. When used, it ensures that the child is in a deep sleep state during the entire examination. Compared with the 2 ml gas injection gradient of the Meinds research team, it also has a higher accuracy rate [12]. In addition, this study has greatly reduced the dependence on the operator's experience by formulating a unified and standardized result judgment standard, clarified the extent of the decline in RAIR, and at the same time avoided the false positives caused by the occasional RAIR caused by children's activities. Of course, the attention to detail during the operation and the desirability of sedation methods [18] are still a strong guarantee for the accuracy of diagnosis.

Studies have shown that the negative predictive value of ARM in the diagnosis of HD is 100% [12, 14]. Unlike them, the specificity of ARM in the diagnosis of HD in this study was only 65%, and only 85% of children with positive RAIR on ARM examination were eventually diagnosed as not HD. This difference stems from the differences in the research objects and methods of this study. In this study, most of the children with RAIR positivity in ARM almost ruled out HD based on the clinical experience of doctors. Therefore, RSB examinations were not performed in this part of the children. Children without the gold standard control were not

included in the study; therefore, the specificity of this study was low. However, this is also one of the advantages of this study. All the included research subjects underwent RSB and ARM examinations at the same time. The research method of comparing the difference between the two examination results of the same individual has a higher degree of credibility.

Consistent with the results of de Lorijn [2], this study also confirmed that the sensitivity and specificity of the HD diagnosis of ARM in the population between 28 days and 6 months of birth were not significantly different from those of the entire group of children. However, the use of ARM in neonatal populations in existing studies is still controversial [2, 9]. In this study, ARM diagnosed neonatal HD with almost no missed diagnosis, but the misdiagnosis rate was as high as 67%. Compared with children of other age groups, the diagnostic sensitivity is almost the same, but the specificity is significantly lower than other age groups. The reasons for the analysis may be as follows. First, RSB may not be appropriate as the gold standard for the diagnosis of neonatal HD. Studies have shown that neonatal enteric ganglion cell dysplasia may cause false positive results [19], so the reliability of the conclusion of RSB as the gold standard diagnostic test for neonatal HD would be questioned. Second, the sample size of newborns in this study was only 13, and the insufficient sample size may cause the results to be biased. This is also the limitation of this study. Therefore, we will continue to carry out this study to expand the sample size of the newborn population. At the same time, we will use intraoperative pathological slices or clinical follow-up results as the gold standard for the diagnosis of neonatal HD and further explore the application value of RSB and ARM in screening and diagnosing HD in the newborn population.

5. Conclusion

ARM is a viable screening tool for HD. It has high sensitivity in children with HD at all ages. However, in the neonatal population, ARM diagnoses HD with higher false positives, and clinicians need to combine the clinical symptoms of the children with RSB results to further confirm the diagnosis. Of course, it is also necessary to develop a more reasonable diagnostic gold standard for newborns to further explore the diagnostic value of ARM in the newborn population for HD.

Declarations

Author contribution statement

Yuanyuan Liang: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Ting An: Performed the experiments.

Wenqiong Xin: Contributed reagents, materials, analysis tools or data.

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The authors do not have permission to share data.

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The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

- [1] D.M. Liang, F.H. Chen, X.L. He, The effect of continuous nursing on the behavioral and psychological state of children with Hirschsprung's disease, *Chin. J. Pract. Nurs.* 15 (2013) 26–28.
- [2] F. de Lorijn, L.C. Kremer, J.B. Reitsma, et al., Diagnostic tests in Hirschsprung disease: a systematic review, *J. Pediatr. Gastroenterol. Nutr.* 42 (5) (2006) 496–505.
- [3] J. MR, K. Gé-Ann, P. Kevin, et al., Infant's age influences the accuracy of rectal suction biopsies for diagnosing of Hirschsprung's disease, *Clin. Gastroenterol. Hepatol.: Off. Clin. Prac. J. Am. Gastroenterol. Asso.* 13 (10) (2015).
- [4] F. Florian, P. Prem, Rectal suction biopsy for the diagnosis of Hirschsprung's disease: a systematic review of diagnostic accuracy and complications, *Pediatr. Surg. Intern.* 31 (9) (2015).
- [5] A.E. Bharucha, Pelvic floor: anatomy and function, *Neuro Gastroenterol. Motil.* 18 (7) (2006).
- [6] S. Louise, L. Tj, H.J. Alex, et al., Differential sphincteric studies in the diagnosis of ano-rectal disorders of childhood, *J. Pediatr. Surg.* 2 (6) (1967). W.B. Saunders.
- [7] L. Jon, H.H. N, Anal canal pressures in the diagnosis of Hirschsprung's disease, *J. Pediatr. Surg.* 2 (6) (1967). W.B. Saunders.
- [8] Prem Puri, *Hirschsprung's Disease and Allied Disorders*, Springer, Cham, 2008.
- [9] N. Iwai, J. Yanagihara, K. Tokiwa, et al., Reliability of anorectal manometry in the diagnosis of Hirschsprung's disease, *Z. Kinderchir.* 43 (6) (1988) 405–407.
- [10] A. Nagasaki, K. Sumitomo, T. Shono, et al., Diagnosis of Hirschsprung's disease by anorectal manometry, *Prog. Pediatr. Surg.* 24 (1989) 40–48.
- [11] J. Yokoyama, T. Kuroda, H. Matsufugi, et al., Problems in diagnosis of Hirschsprung's disease by anorectal manometry, *Prog. Pediatr. Surg.* 24 (1989) 49–58.
- [12] R.J. Meinds, M. Trzpis, P.M.A. Broens, Anorectal manometry may reduce the number of rectal suction biopsy procedures needed to diagnose Hirschsprung disease, *J. Pediatr. Gastroenterol. Nutr.* 67 (3) (2018) 322–327.
- [13] Y.T. Chen, X.L. Gu, Diagnosis and treatment status of children with functional constipation, *Chin. J. Pract. Pediatr.* 16 (10) (2011) 622–624.
- [14] X. Liu, The application value of anorectal manometry in the diagnosis of Hirschsprung's disease, *J. Indust. Enterp. Med.* 12 (1) (1999) 6–7.
- [15] Y.X. She, X.R. Shi, Diagnosis of Hirschsprung's disease by anorectal manometry and histochemistry-A report of 31 cases, *J. Shanghai Sec. Med. Col.* (1) (1981) 53–57.
- [16] S. Tamate, C. Shiokawa, C. Yamada, et al., Manometric diagnosis of Hirschsprung's disease in the neonatal period, *J. Pediatr. Surg.* 19 (3) (1984) 285–288.
- [17] X.P. Zhang, M. Wu, X.L. Zhou, Application and nursing of anorectal manometry in Hirschsprung's disease, *Chin. J. Pract. Nurs.* 20 (9B) (2004) 39–40.
- [18] Y.Y. Liang, X.T. Wan, T. An, et al., Comparison of the sedative effects of two chloral hydrate administration routes for anorectal pressure measurement in children under 4 years of age, *J. Clin. Pathol. (Lond.)* 41 (9) (2021) 2101–2106.
- [19] A.M. Holschneider, E. Kellner, P. Streibl, W.G. Sippell, The development of anorectal continence and its significance in the diagnosis of Hirschsprung's disease, *J. Pediatr. Surg.* 11 (2) (1976) 151–156.