ORIGINAL ARTICLE

DOI: 10.34057/PPj.2021.40.02.006
Pelviperineology 2021;40(2):96-102

# Diagnosis and pathophysiology of Hirschsprung's disease

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## ABSTRACT

**Objective:** The aim of this research was to study the X-ray findings of Hirschsprung's disease (HD) based on analysis of radiographs and videos published on the Internet and our own research, in order to increase the accuracy of X-ray diagnosis HD.

**Materials and Methods:** An analysis of 56 radiographs and 2 videos of patients with a histologically confirmed diagnosis of HD was performed, including 25 radiographs from our own practice and 31 radiographs and 2 videos from articles published in PubMed and PMC. For comparison, cases without HD were compared, including radiographs from the author's practice, where HD was excluded based on manometric detection of rectoanal inhibitory reflex (RAIR). For X-ray analysis, a contrast marker of known diameter was used, which was located near the anus.

**Results:** In addition to the signs already described in the literature (the transition zone, microcolon, retention of contrast on post evacuation film, and the rectosigmoid ratio <1), we propose new anatomical signs of HD, i.e. the absence of an anterior displacement of the anal canal axis, an expansion of the retro-rectal space, and symptom of "frozen" segmentation. In addition, we suggest novel physiological diagnostic signs, i.e. the absence of the RAIR and defecation reflex.

**Conclusion:** The combination of these signs makes it possible to diagnose HD. Shortening of the anal canal, with a noticeable displacement of it towards the pubis, as well as the presence of RAIR and wide opening of the anal canal during rectal emptying indicate the absence of HD. The use of these signs increases the accuracy of the HD diagnosis. An algorithm of diagnostics is offered.

**Keywords:** Anal manometry; Hirschsprung's disease; congenital aganglionosis; x-ray diagnosis

## INTRODUCTION

Hirschsprung's Disease (HD) is relatively common in children. Surgical treatment is aimed at removing the aganglionic section of the gut and repairing the intestinal tract. Despite some achievements of recent years, the diagnosis of the disease is not always timely. After surgical correction, functional problems may arise.[1] The final diagnosis of HD is based on rectal biopsy. Nevertheless, the diagnostic process may involve a contrast barium enema, which in some cases allows to reject the putative diagnosis of HD, and in 70%–90% of cases establish the location of the transition zone.[2] Some authors recommended the use a manometric study to exclude HD, but its use is recently decreasing.[3]

During normal early embryonic development, the nerve cells invade the primary intestine in a craniocaudal direction. The enteric ganglia are interconnected to form two plexuses that extend along the length of the bowel: an outer myenteric (Auerbach) plexus - running through the full length of the gut, and an inner submucosal (Meissner) plexus, found only in the small and large intestine. The myenteric plexus develops first and

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**Received:** 11 May 2021 **Accepted:** 11 May 2021

is situated between the longitudinal and circular smooth muscle layers. It is involved in intestine motility, while the submucosal plexus, which is formed later, regulates motility, blood flow, and the transport of ions across the intestinal epithelium.[4]

Gut motility is controlled by interdependent mechanisms including neural, such as the enteric ganglia, and nonneural, such as the interstitial cells of Cajal (ICC).[4,5] The ICC serve as pacemaker cells creating and propagating slow waves that lead to smooth muscle contraction in the gut.[4]

The absence of enteric ganglion cells of the myenteric and submucosal plexus along variable portions of the gastrointestinal tract results in HD, which is characterized by sustained contraction of the aganglionic bowel segment, leading to intestinal obstruction and distension of proximal segments (megacolon). No matter how far from the anus the aganglionic segment begins, it always reaches the middle of the anal canal. The gold standard for an HD diagnosis is a rectal biopsy.[5]

In 80%–85% of HD cases, the aganglionic region is limited to the rectum and sigmoid colon. Long segment disease occurs in up to 20% of cases and is characterized by aganglionosis extending proximally to the sigmoid colon. Total colonic aganglionosis is rarer, occurring in 3%–8% of patients with HD. Another rare variant is ultra-short segment disease, affecting only the distal rectum (≤2 cm).[5,6]

## Anorectal Manometry (ARM)

During anorectal manometry (ARM), a flexible catheter, with a non-latex balloon at its distal end, is introduced into the rectum. The sensor measures intra-anal pressures during the study. The recto-anal inhibitory reflex (RAIR) is the reflex relaxation of the internal anal sphincter (IAS) in response to rectal distention. This reflex is present in individuals with normal intrinsic innervation of the intestine (Figure 1a) and is absent in those with HD. The HD is characterized by a short-term rise in pressure in the upper anal canal in response to rectal dilatation (Figure 1b, c). The depth and duration of the relaxation of the IAS progressively increases with the increasing in the rectal balloon volume up to 70 cm³ and thereafter does not change (Figure 1c).[7,8] In a study by Jarvi et al.[9] the specificity and positive predictive value of ARM for HD were 83% and 80%, respectively. They concluded that if RAIR is present, a rectal biopsy may not be required.

Radiologic anatomical findings with contrast enema that are suggestive of HD include the presence of a radiographical transition zone with proximal dilated bowel, microcolon, retention of contrast material on the post evacuation film, irregular colonic contractions, mucosal irregularity, and an abnormal rectosigmoid ratio. The radiographic location of the transition zone has been shown to correlate with the length of the aganglionic segment, specifically of the rectosigmoid segment. The findings may aid in the surgical procedure planning. However, the correlation was low in segments proximal to the rectosigmoid colon and in children younger than 3 months of age. This further highlights the importance of intraoperative biopsies to direct surgical planning.[5] In a systematic review of the literature, de Lorijn et al.[10] reported that contrast enema had lower mean sensitivity and specificity of 70% and 83%, respectively, when compared to ARM and rectal suction biopsy. Furthermore, contrast enema in the neonatal period has been shown to be less reliable than in older children.[10]

## Radiologic functional findings

Nusslé et al.[11] showed for the first time the X-ray manifestation of the RAIR during a contrast enema in the form of penetration of the contrast medium into the upper part of the anal canal. Measurement of anal pressure during a barium enema revealed that the penetration of barium into the upper part of the anal canal in front of the tip of the enema is accompanied by a decrease in anal pressure, and after the disappearance of barium from the anal canal, anal pressure is restored to the basal level. The use of a contrast marker near the anus improves visualization of the X-ray equivalent of the RAIR.[12]

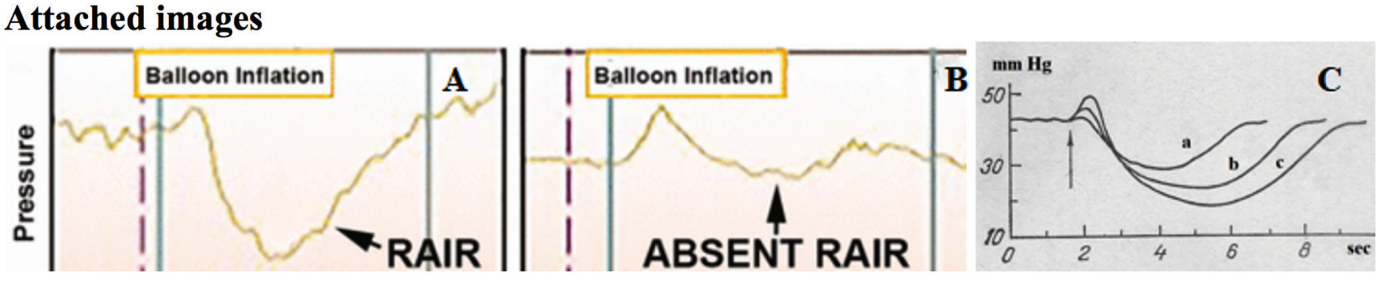


**Figure 1.** Anorectal manometry. Representative single sensor pressure tracings from different individuals with a normal RAIR (**A**) and a patient with HD (**B**). From an article by Ambartsumyan et al[5]. (**C**) Graphs anal pressure (RAIR) following rapid injection of air into the rectum: (a) 30 cm³; (b) 50 cm³; (c) 70 cm³.[8]
*RAIR: Rectoanal inhibitory reflex*

Ornö et al.[13] applied sonographic method for examination of the RAIR. The RAIR was elicited by injecting 20 ml water into the rectum, and the events in the bowel were recorded on video for offline analysis. Among 28 children (median age, 21 months; range, 5 days–12 years; 11 younger than 1 year and 7 between 1 and 2 years) with suspected HD, in 3 with aganglionosis, RAIR was absent. In 17 children, the RAIR was present, and all of these children had normal histologic findings. In eight children, sonography did not show the reflex despite normal histologic findings (29% false-negative results).[13] Vult von Steyern et al.[14] used an enema with Omnipaque 140 mg/ml for the differential diagnosis of chronic constipation. After the contrast medium had filled the rectum and the distal part of the sigmoid, two sequential fast (<5 s) injections of 20 ml cold contrast agent (16 °C) were performed with documentation of low pulse fluoroscopy sequences for about 30 seconds each. The contrast medium was injected until a transition zone was identified or the whole colon was filled. Five boys and one girl (median age, 7.5 days) were diagnosed with HD. The negative predictive value of the RAIR was 100%. A contrast enema with signs of HD in combination with an absent RAIR had the specificity of 98% and sensitivity of 100% for HD.[14]

In HD, apart from the absence of RAIR, there is no information about the function of the external anal sphincter (EAS), puborectalis muscle (PRM), and levator plates (LP). This information can be useful for improving the accuracy of the preoperative diagnosis, as well as for choosing the optimal method of surgical treatment.

The aim of this research is to study the X-ray symptomatology of HD, based on analysis of radiographs and videos published on the Internet and based on our own research to increase the accuracy of X-ray diagnosis HD.

## MATERIAL AND METHODS

An analysis of 56 radiographs and two videos of patients with a histologically confirmed diagnosis of HD was performed, including 25 radiographs from our own practice and 31 radiographs and two videos from articles published in PubMed and PMC. In 18 articles, only frontal radiographs were given. Lateral radiographs have been reported in 13 articles, mostly in the past 20 years. As examples of cases without HD, radiographs from our own practice are given, where HD was excluded based on RAIR detection in the manometric examination. For X-ray analysis, a contrast marker of known diameter was used, which was located near the anus. This made it possible to measure the length of the anal canal, as well as to determine the true parameters of different parts of the intestine, which were compared with previously published age standards.[12]

## RESULTS

### Frontal and lateral images

In many cases, a frontal radiograph is sufficient to diagnose HD and determine the level of the transition zone (Figure 2a). However, in some patients, a frontal radiograph may be unreliable. The short aganglionic segment may be obscured by an extended rectum. To visualize it, a lateral radiograph is required (Figure 2b).

In infants, the difference in width between healthy and aganglionic segments may be negligible. A lateral radiograph and X-ray study of the RAIR may be diagnostic (Figure 3).

### X-ray analysis

The anus is located where the contrast agent has stained the buttocks around the catheter (asterisk). The true length of the anal canal (e), located between the pubococcygeal line and the anus, is 1.7 cm at this age.[15] Based on this, the width of the distal rectal segment is 0.6 cm (the minimum normal limit for this age is 1.3 cm). Thus, using the radiologic analysis, the “microcolon” symptom received a digital expression. The retro-rectal space, i.e. the distance from the posterior wall of the rectum to the vertebra (red line) is 0.8 cm while the size appropriate to the age should not exceed 0.1 cm. Therefore, this finding depicts a sharp narrowing of the rectum and a sharp expansion of the retro-rectal space. Throughout the study, the axes of the rectum and the anal canal completely coincide. This means that the PRM did not contract and not pull the upper part of the anal canal anteriorly. During the emptying of the contrast medium, the rectum did not participate in this process, and there was no expansion of the anal canal, i.e. there was no contraction in levator plates. Three segments of the rectum expanded and moved caudally, but retained the same shape - a symptom of

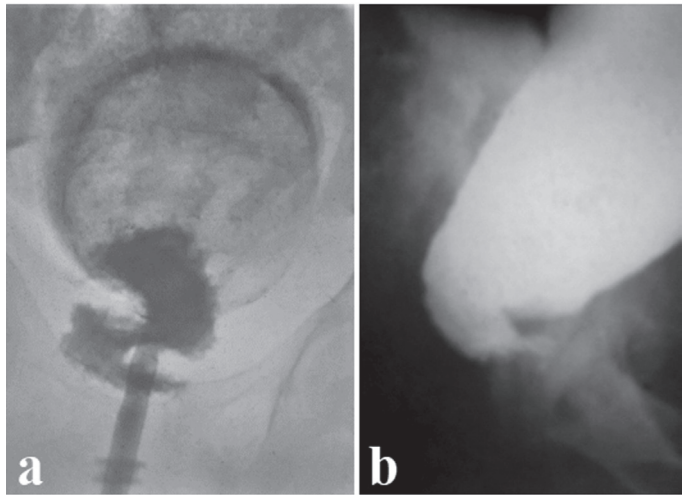


**Figure 2.** Frontal (**a**) and lateral (**b**) radiographs patients with HD
*HD: Hirschsprung’s disease*

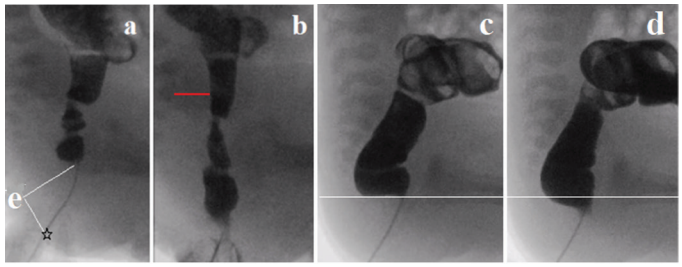


**Figure 3.** Video excerpts from von Steyern's article[14] with permission from the authors. A 1-month-old boy later diagnosed with Hirschsprung disease. The rectoanal inhibitory reflex is absent. At the beginning of the study (**a**), the contrast agent in the rectum was divided into 3 segments by circular contractions. ("e" - anal canal). The end of the catheter is located between the upper and middle segments. As a result of the introduction of a contrast agent, the volume in the lower segments increased, which indicates an increase in pressure. Then (**b**) segments (symptom of frozen segmentation) partially moved into the anal canal. There is a sharp expansion of the retro-rectal space (red line). (**c-d**) A 1-month-old boy without Hirschsprung's disease. The rectum is wide with smooth walls. The axis of the anal canal is displaced anteriorly from the rectum. During the injection of the contrast agent, it penetrated into the upper part of the anal canal (RAIR)
*RAIR: Rectoanal inhibitory reflex*

frozen segmentation. Consequently, emptying occurred without a defecation reflex. Thus, the lack of relaxation of the IAS was not the only symptom of HD.

This analysis indicates that in order to improve the diagnosis of HD, it is necessary to perform at least frontal and lateral radiographs. Video, frontal radiograph at 24$^{th}$ hours, and radiometric analysis of radiographs may confirm the diagnosis once there were doubts after standard radiography.

## The sign of the rectosigmoid ratio <1 (Figure 4).

### X-ray analysis

In Figure 4a, the rectum proximal to the short contracted aganglionic segment (d) is narrower than the sigmoid colon, and the question may arise, is it aganglionic? Measurement shows that it is much wider than the maximum normal limit. The rectum to sigmoid ratio <1 is due to the fact that expansion of the rectum is limited by the size of the small pelvis, while the expansion of the sigmoid colon is not limited. In Figure 4b, the rectosigmoid ratio is <1 for the same reason. However, a sharp shortening of the anal canal is indicative of stretching of the pelvic floor muscles, which is called "perineal descending syndrome" - characteristic of functional constipation. In all 12 patients with HD, where it was possible to measure the length of the anal canal, including five patients with a short form of aganglionosis, the length of the anal canal was within the age norm.

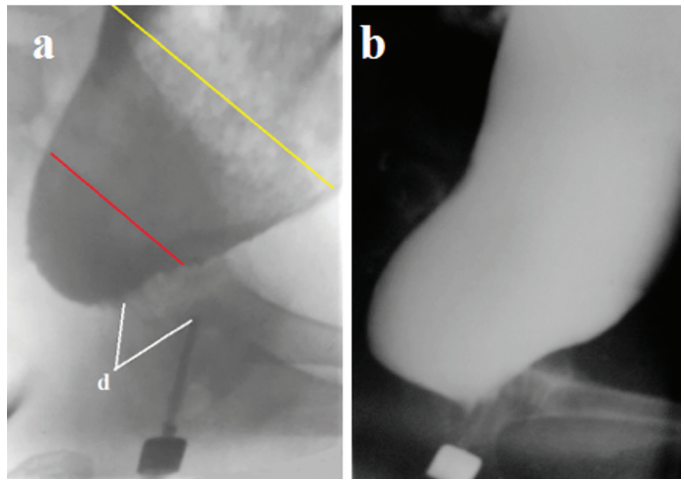


**Figure 4.** (**a-b**) Rectosigmoid ratio in HD and in FC. (**a**) A 10-year-old girl with a short (d = 2.5 cm) aganglionic segment, which is in a contracted state. The width of the rectum (red line) is 6.4 cm. A maximum age norm is 4.1 cm. The width of the sigmoid colon is 11 cm. A maximum norm is 2.6 cm). (**b**) An 8-year-old male with FC. He has a rectosigmoid ratio <1. However, the rectal width is 5.1 cm. It greater than the maximum normal limit (4.1 cm), and the anal canal length of 1.4 cm is significantly less than the minimum normal limit (2.6 cm)
*HD: Hirschsprung's disease; FC: Functional constipation*

Analysis of radiographs shows that expansion of the rectum above the normal limit in combination with shortening of the anal canal may be characteristic only of functional constipation and not of HD.

Irregular colonic contractions and mucosal irregularity are optional signs of HD. Colonic and/or rectal narrowing and segmentation, as well as mucosal irregularity, may be signs of enterocolitis. Enterocolitis is a sequale of intestinal obstruction and in turn, makes it worse. Usually, not all segments of the intestine are narrowed and involved in the inflammatory process. Consequently, the rectum may have a normal width and contour (Figure 5a). However, its shape differs sharply from the normal one. Due to the absence of nerve ganglia in the rectum, an increase in pressure in it does not cause relaxation of the IAS and does not cause a reflex contraction of the PRM and EAS. As a result, there is no dislocation of the lower part of the rectum forward and no horizontal branch of the rectum is formed.

The aganglionic segment of the intestine may be in a spastic state during the inflammatory process. Without enterocolitis, its width can be within normal limits. In such cases, the sigmoid colon is expanded due to stasis of the stool throughout the rectum since there is no peristalsis in it. In HD, unlike functional constipation, the rectum is not dilated, the length of the anal canal is not shortened and there is no RAIR. An additional symptom of HD is the lack of signs of PRM contraction. Normally, the axis of the anal canal coincides with the rectal axis only in

infants. In older children, the periodic contraction of the PRM pulls the upper part of the anal canal toward the pubis during the fecal retention. Then, a horizontal branch of the rectum is formed, the axis of the anal canal is displaced anteriorly and an acute recto-anal angle may be formed (Figure 5b). Four patients demonstrated an absence of a horizontal branch of the rectum with merge of the axes of the rectum and the anal canal. They all had a rectosigmoid ratio <1. The rectum was not narrow but not above the normal limits. We consider this combination of signs typical for HD because in our practice we have never observed it with other diseases. These findings may suggest that the rectum is not connected by nerve pathways with the PRM and therefore the expansion of the rectum does not cause a reflex contraction of the PRM, as it normally happens about seven times per hour.

In four patients with HD, the radiographs show a small displacement of the anal canal axis anterior to the rectum (Figure 5c) with a short horizontal rectal ramus. This is because the posterior wall vertical branch of the rectum remains next to the coccyx, while with age, the size of the perineum increases, and the distance between the coccyx and the anus increases. If the rectum had a normal width, then the axis of the anal canal would pass through the rectum. The measurement of the horizontal distance between the last coccygeal vertebra and the ano-rectal junction was found to be the same in patients with HD of the same age (see Figures 5b, c - red line). The presence of an ano-rectal angle of more than 90 degrees in each case, confirms the assumption that there is no contraction in the PRM.

In HD, unlike as in functional constipation, the rectum is not dilated, the length of the anal canal is not shortened and there is no RAIR. An additional radiologic sign of HD is the lack of signs of PRM contraction: (1) the absence of a horizontal branch of the rectum with the coincidence of the axes of the rectum and the anal canal; (2) the absence of a penetration of contrast agent into the anal canal in front of the tip of the enema. These signs also suggest that the aganglionic rectum is not connected by nerve pathways with the PRM.

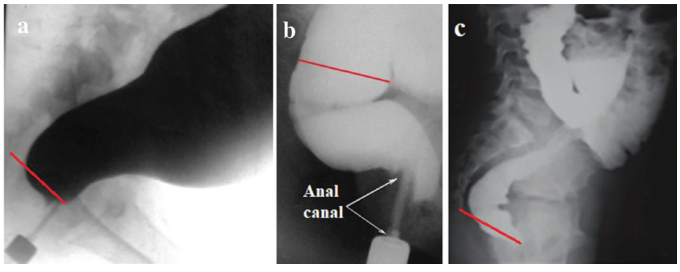


**Figure 5.** Lateral radiographs of the ano-rectum of patients at the age of 4–6 years. The true diameter of the marker located near the anus is 1.6 cm. *IAS: Internal anal sphincter; RAIR: Rectoanal inhibitory reflex; HD: Hirschsprung's disease; Prm: Puborectalis muscle*

## DISCUSSION

As shown in a systematic review de Lorijn et al.[10], the sensitivity and specificity of contrast enema (12 studies for a total of 425 patients) were significantly lower than those of anorectal manometry and rectal suction biopsy, with mean sensitivity and mean specificity of 70% and 83%, respectively. According to Wong et al.[18], the sensitivity of the 24 hours of delayed film was 85.7 % and the specificity was 17.6%. The diagnosis of HD is actually based on four radiologic anatomical signs: A transition zone with proximal dilated bowel, microcolon, retention of contrast in the post evacuation film, and an abnormal rectosigmoid ratio (<1). As shown above, none of these signs are 100% reliable. An increase in the diagnostic accuracy of a contrast enema can be achieved in three ways: (1) optimization of the examination program; (2) comparison of radiographic images of ano-rectum with normal specimens of anorectal anatomy; (3) studies of anorectal reflexes.

### Optimization of the patient examination program includes the following provisions

a) Contrast agent. For chronic constipation with signs of acute deterioration, a water-soluble contrast agent is preferred. In other cases - a barium enema.

b) Using a contrasting mark of a known diameter on the tip of the enema, which touches the anus allows to measure the length of the anal canal, determine the location of its axis, and use radiometric analysis to compare the obtained data with age standards.[1] This made it possible to define the concept of "microcolon" as the width of the rectum and of the colon is less than the minimum age limit.[2] A decrease in the length of the anal canal relative to the minimum age limit makes it possible to reliably exclude HD.[3] The absence of the lower horizontal branch of the rectum in a patient older than a year, is characteristic of HD at the non-dilated rectum, and the rectosigmoid ratio <1.

c) The lateral radiograph and/or the video recording, allows to fixate the relaxation of the IAS (RAIR).[4] Penetration of the contrast agent into the anal canal in front of the enema tip indicates relaxation of the BAC. This is aradiologic manifestation of the RAIR. The presence of the reflex reliably excludes HD, to the same extent as in ano-rectal manometry. At the same time, the reliability of the radiologic functional method for determining RAIR is not inferior to the manometric method, and even surpasses it. In a study by Jarvi et al.[9], the specificity and positive predictive value of ARM for HD were 83% and 80%, respectively. A contrast enema with signs of HD in combination with an absent RAIR had the specificity of 98% and sensitivity of 100% for HD.[14]

d) If on the radiograph after emptying and/or after 24 hours, the contrast agent remains above a narrow or spasmodic intestinal

segment, this is suspicious of HD. However, if this is combined with the symptom of "frozen" segmentation, i.e., segmentation of the intestine that does not change over time, it indicates the absence of peristalsis and therefore is a convincing sign of HD. As can be seen from Table 1, a combination of several signs increases the accuracy of the differential diagnosis between HD and functional constipation ("without Hirschsprung's disease"). At the same time, the detection of normal anorectal reflexes (RAIR and/or defecation reflex) allows excluding HD and avoiding rectal biopsy.

## CONCLUSION

As shown by numerous studies, four radiologic anatomical signs [transition zone with proximal dilated bowel, microcolon, retention of contrast on post evacuation film, and an abnormal rectosigmoid ratio (<1)] have low sensitivity and specificity in the differential diagnosis of the HD and functional constipation. The use of the X-ray functional signs described by us increases the reliability of X-ray diagnostics. The present study has shown that the aganglionic rectum does not have neural connections with anorectal sphincters. Therefore, an increase in rectal pressure does not induce relaxation of the IAS, a contraction of the PRM, external anal sphincter, and levator plates.

### Ethics

**Ethics Committee Approval:** Ethics committee approval is not necessary for this type of studies.

**Informed Consent:** Since this study does not involve human subjects informed consent is not necessary.

**Peer-review:** Externally peer-reviewed.

## DISCLOSURES

**Financial Disclosure:** The author stated that they had no relevant financial interests or personal affiliation.

**Table 1. Significance of radiologic signs in diagnosis of Hirschsprung's disease**

| X-ray symptoms | Hirschsprung's disease | | Without Hirschsprung's disease |
|---|---|---|---|
| | 100% | Doubtful symptom | 100% |
| Obvious transition zone with distal microcolon | x | | |
| Rectosigmoid index <1 with non-dilated rectum | x | | |
| Rectosigmoid index <1 with dilated rectum | | x | |
| Rectosigmoid index <1 with dilated rectum and anal canal shortening | | | x |
| Rectosigmoid index <1 without horizontal branch of the rectum | x | | |
| Symptom of "frozen" segmentation | x | | |
| Expansion of the retro-rectal space | | x | |
| Shortening of the anal canal | | | x |
| Relaxation of IAS (RAIR) | | | x |
| Defecation reflex (wide opening of the anal canal) | | | x |

IAS: Internal anal sphincter; RAIR: Rectoanal inhibitory reflex

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