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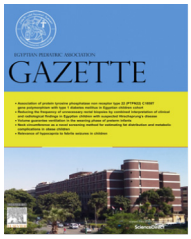

Reducing the frequency of unnecessary rectal biopsies by combined interpretation of clinical and radiological findings in Egyptian children with suspected Hirschsprung's disease

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KEYWORDS

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Abstract *Introduction:* Hirschsprung's disease (HD) should be considered in children with neonatal-onset constipation. Clinical differentiation between HD and idiopathic constipation (IC) is difficult in late presenting infants. Consequently, paediatric surgical centres receive numerous referrals for rectal biopsies, requiring admissions and GA, particularly if suction biopsy is unavailable, and in older children.

Methods: Forty-two cases referred for rectal biopsy, were studied for clinical features, single contrast enema, as compared to rectal biopsy findings, to determine the statistical reliability towards achieving a diagnosis.

Results: The mean age at presentation was 106 days in HD patients, and 172 days in IC. Significant neonatal clinical features were present in 54%. Delayed passage of meconium was present in 86% of HD, compared to 14% of IC ($p = 0.001$). Rectal examination found a tight segment in 90% of HD, and a distended anorectum in 64% of IC ($p = 0.005$). The sensitivity of contrast enema was 86%,

Abbreviations: HD, Hirschsprung's disease; IC, idiopathic constipation.

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and the specificity was 90%. The histological analysis of strip rectal biopsy was sensitive in 93%, and inconclusive in 7%.

Conclusion: This audit generated a checklist of 6 clinical and 3 radiological criteria, to differentiate HD from ID, including *clinically* (1) neonatal onset; (2) male sex; (3) congenital anomalies, dysmorphic features and/or family history of HD; (4) delayed meconium passage; (5) enterocolitis or significant bowel obstruction/impaction; (6) tight segment on rectal examination; and *radiologically* (7) funnelled transition zone or a reversed rectosigmoid index (<1); (8) delayed evacuation of contrast after 24 h; and (9) absent distension of the anorectum with contrast, absent mucosal irregularities, and absent sigmoid looping.

Introduction

Hirschsprung's disease (HD) remains a challenging diagnosis to the paediatric surgeon. It should be considered in any early-onset constipation and difficult passage of stools. It is generally an isolated disorder of full-term otherwise healthy infants.[1]

The absence of ganglion cells from the distal intestine is the hallmark of the disease. Ganglion cells are missed from both the submucosal and inter-muscular nerve plexuses. In addition, there is a marked increase in the nerve fibres extending into the submucosa. Aganglionosis typically extends up to the recto-sigmoid region in approximately 80% of cases.[2]

It has been reported that 90% of HD patients could be diagnosed before the age of one month, and if not during the neonatal period, mostly by the age of one year.[3,4] Classic rectosigmoid segment HD has a male to female ratio of 4:1,[5] but this male to female predilection declines in the more proximal forms, compared to the classic pattern.[6]

Most HD cases present with delayed passage of meconium. Some reports stated a wide range of the incidence of this finding, varying between 60% and 94%.[4] It may surprisingly fail to differentiate HD from idiopathic constipation (IC), as some reports found it in only 65% of HD patients, versus 13% in IC patients.[3]

Chronic constipation, dependency on laxative suppositories, straining during defecation, noticeable abdominal distension, hard stools, and occasionally blood-streaked stools are features of both HD and IC, and it could be difficult at times to differentiate clinically between both groups without further investigation. It could be generally stated that infants presenting beyond the neonatal period have a higher incidence of not being HD, hence their dietary and medical management should be attempted thoroughly.[7]

An early diagnosis of HD is important as there is a present consensus of operating on HD during the neonatal period or shortly after, to avoid the myriad of complications that occur in untreated cases, as well as the general concept that the operation could be technically easier in neonates.[9]

The rectal biopsy, traditionally a full-thickness biopsy, is the gold standard for the diagnosis of HD. Suction rectal biopsy has been widely adopted, and is reported to have an accuracy of more than 90%.[9] Yet, when the diagnosis cannot be made by suction rectal biopsy, a full-thickness posterior rectal wall biopsy should be performed in the operating room. The pathologic evaluation of a suction biopsy for the diagnosis of HD is considerably more difficult than that of full thickness biopsy and needs a highly skilled pathologist.[10]

There have been some attempts at studying the sensitivity and specificity of the various clinical data and noninvasive investigations aiming at reducing the performance of unnecessary rectal biopsies, which are believed not to be without complications. This hypothesis was based on reports that only 12–17% of biopsies performed on constipation patients yielded a positive result of aganglionosis and that up to 80% of biopsies could be unnecessary.[10,11]

As contrast enema is a non-invasive diagnostic tool, the presence of suggestive enema findings associated with a classic clinical presentation is pathognomonic, and warrants a surgical referral and involvement. It is the opposite situation that may need a suggested algorithm, or a scoring system, when both the clinical and contrast enema findings are equivocal.

This current work analysed the statistical significance of the available clinical and radiological parameters, and investigated the reliability of these diagnostic tools. We aim not at substituting absence of ganglion cells in a rectal biopsy, as the sole indication to do a pull-through operation, but rather to properly select the patients that need a rectal biopsy within the context of management of resources for very busy paediatric surgical services in the developing world.

Methods

Forty-two patients presenting with chronic persistent constipation, referred to the paediatric surgeons for a rectal biopsy, after having a contrast enema, were retrospectively studied. The patients were enrolled over a period of 6 months from January 2013 to June 2013.

We statistically analysed the clinical assessment of the enrolled patients including the age at presentation, neonatal onset of symptoms, consanguinity, maturity at birth, antenatal history, associated congenital anomalies, delayed passage of meconium, nutritional status, vomiting, feeding difficulties, features of enterocolitis or significant bowel obstruction, abdominal distension, and the digital per-rectal examination.

Similarly we statistically analysed the radiological features of the contrast enema including the presence of a funnel-shaped transition zone, recto-sigmoid index (ratio of the rectal diameter to sigmoid diameter, normally $\geqslant 1$, and considered reversed and thus suggestive of HD if <1), residual contrast in the colon after 24 h, distension of the anorectum with contrast, abnormal colonic contractions or spasms, mucosal irregularities, serrations, sigmoid looping and redundancy. The interpretation of the contrast enema was done by both an

experienced paediatric radiologist, together with a paediatric surgeon, within an MDT setting.

We generated a checklist of the most statistically significant features clinically and radiologically to be used for screening of similar future cases, in order to select cases that need a further workup, as opposed to cases that only need medical management and watchful observation.

The contrast enema technique was a single contrast method with post evacuation filming, using Barium (Polibar 115%). No colonic evacuation was allowed for three days prior to the study. Infusion of the contrast without forcible pressure was done with intermittent screening.

Rectal strip biopsy was done under a general anaesthetic. Standard Haematoxylin and Eosin stains were used. Adequate submucosal tissue to examine the Meissner's plexus was mandatory to consider the specimen valid. If found inconclusive these specimens were re-evaluated to confirm their deficiency, the biopsy was then repeated, and anorectal manometry was arranged in some instances, if needed.

Results

Patients enrolled in this audit were retrospectively divided into two groups, according to the rectal biopsy result. Group (HD) comprised 28 patients diagnosed as Hirschsprung's disease. Group (IC) comprised 14 patients in which HD have been ruled out.

The mean age at presentation in the HD group was 106 days (range of one standard deviation 2–326 days). The IC group had a mean age at presentation of 172 days (range of one standard deviation 10–355 days). Neonatal onset of features requiring a surgical consultation as constipation, abdominal distension, and vomiting was present in 54% of HD patients, versus 27% of the IC group.

There was no difference in consanguinity, which was 29% in the HD group and 36% in the IC group. Similarly there was no difference in maturity at birth, or antenatal problems, between both groups. The male:female ratio in the HD patients was 4:1, and 2:3 in the IC group.

Three cases (11%) that were eventually diagnosed as HD had associated congenital diseases; one was Down syndrome, one had a syndromic mental retardation, and the third had dysmorphic features and absent Simian crease.

Delayed passage of meconium of 2 days or more was present in 86% of HD cases, compared to two patients with IC (14%) ($p = 0.001$). However, as mentioned above, only in 54% of HD patients was the neonatal presentation impressive to warrant an early referral.

Symptoms suggestive of enterocolitis and/or significant bowel obstruction were found to have occurred at least once in 46% of HD patients. On the other hand 21% of the IC group presented with one episode of similar features, despite being much milder, and could be rather attributed to faecal impaction.

Nutritional impairment, and feeding difficulties did not clearly differentiate either of the two groups and were present in 21% of HD patients, versus 29% of the IC group ($p = 0.5$). Abdominal distension did not differentiate either group clearly as well, as it was present in 70% of HD patients as opposed to 50% in the IC group. The degree of distension was much noticeable (moderate – severe) in the HD group, as compared to being mild in the IC group.

A digital rectal examination found a tight anorectal segment in 90% of HD patients, and a distended anorectum in 64% of IC ($p = 0.005$). Of note that 14% of IC cases had a spastic anal sphincter, that mimicked HD ($p = 0.001$).

We also studied the sensitivity and specificity of the radiological features of the contrast enemas done. A funnel-shaped transition zone was found to be more specific than sensitive for diagnosing HD [sensitivity = 75%, specificity = 96%]. Reversed recto-sigmoid index (< 1) was contrarily more sensitive than specific [sensitivity = 93%, specificity = 64%]. Delayed evacuation of contrast after 24 h, detected in a delayed X-ray image, was found in all the 11 cases of HD in which it was searched for. Distension of the anorectum with contrast was present in about 80% of IC and was absent in HD. The overall sensitivity of contrast enema for HD was 86%, and the overall specificity was 90% (see Table 1).

Three other radiological features of abnormal colonic function were studied, abnormal colonic contractions or spasms; mucosal irregularities and serrations; and sigmoid looping and redundancy. These were found to be less statistically significant with p values around 0.8–1.

The extent of the aganglionic segment as found in the contrast study is shown in Table 2. In the cases that have been operated upon, this was found to very closely match the histological level of aganglionosis (86%), but this point is beyond the scope of this report.

The histological analysis of strip rectal biopsy was sensitive in 93% of HD cases, and inconclusive in 7%, due to inadequate samples, not containing ample submucosa, that rendered interpretation difficult. The specificity was 86% due to the presence of 2 false positive (aganglionic specimens) in the IC group, likely due to a distally obtained biopsy, from the normally hypo-ganglionic region, proximally adjacent to the dentate line. Anorectal manometry was done to aide the diagnosis of seven cases (17%) where other diagnostic tools were discordant or inconclusive (see Tables 3 and 4).

Table 1 Incidence of various findings of contrast enema in IC and HD.

Parameter	Idiopathic constipation (Number = 14)	Hirschsprung's disease (Number = 28)	p value
Funnelled transition zone	0 (0%)	21 (75%)	0.001
Reversed rectosigmoid index	5 (35.7%)	26 (92.9%)	0.001
Delayed evacuation of contrast	0 (0%)	11 (39.3%)	0.006
Rectal distension	11 (78.6%)	Absent	0.001
Abnormal contractions and spasm of the colon	7 (50%)	15 (53.6%)	0.827
Mucosal irregularities and serrations	6 (42.9%)	12 (42.9%)	1.00
Sigmoid looping and redundancy	9 (64.3%)	17 (60.7%)	0.822

Table 2 Level of aganglionosis in the HD patients group, confirmed following surgery.

Extent of aganglionosis	Number of cases (%)
Long segment	7 (25%)
Rectosigmoid region	20 (71.4%)
Ultra-short segment	1 (3.6%)

The response to laxative and dietary treatment was adequate for 57% for the IC cases within 6 months; the remaining 43% were resistant and required prolonged treatment.

Discussion

It is not always an easy task to clinically differentiate between HD and IC. As presented in our results, there were few clinical features that exclusively marked either of the two groups.

Other investigators only had 18% of their HD patients manifesting the full triad of delayed passage of meconium, abdominal distension and vomiting. They found as well that 64% of the constipation group had one of these three features.[3] In the current study we found 40% of the HD patients' group presenting this full triad, and only 57% of the constipation group with any of these three findings. This suggested that most cases of IC could be ruled out of the need for rectal biopsy, based on non-invasive clinical tools.

Previous attempts to reduce unnecessary rectal biopsies relied on two clinical findings, delayed passage of meconium and tight anus on examination, and two non-invasive investigations, the barium enema and the rectal manometry.[10,11] In our protocol we preferred to rely preferentially on clinical criteria to reduce the radiation exposure in contrast enema if possible. It was not practical to include anorectal manometry in our protocol as a routine, as it may be difficult to organise and interpret, and does have a questionable reliability if not performed by experienced specialists.[12]

The overall sensitivity of the contrast enema in our study was 85.7% and the overall specificity was 90%. These numbers are comparable to recent reports stating sensitivity and specificity of 76% and 97%.[13] Some reports mentioned a false negative rate of contrast enema ranging from 20% to 28%[14,15]; however, the rate of false negative cases in our study was 14.3%. This shows that at least within our setting, the results of the contrast enema are well correlated and comparable to the rectal biopsy in the diagnosis of HD.

Preoperative radiological assessment conducted in our study to determine the length of the aganglionic segment was comparable to the operative findings in 86% of the operated cases. This figure is nearly similar to that mentioned by Proctor et al. being 90%.[16] We believe this is an interesting point that warrants further work, and is beyond the purpose of the current report.

Table 3 Diagnostic accuracy of rectal biopsy for Hirschsprung's disease.

True positive	93% (26/28)	Sensitivity	93%
False negative (inconclusive)	7% (2/28)	Specificity	86%
True negative	86% (12/14)	Positive predictive value	93%
False positive (aganglionic)	14% (2/14)	Negative predictive value	86%

This study showed a total of 4 cases in both groups (10%) of initially inconclusive or less than satisfactory rectal biopsy specimens. This number dictates the recommendation of performing the biopsy via a well-trained paediatric surgeon. Full thickness rectal biopsy had an overall sensitivity of 93% and specificity of 85.7%. De Lorijn et al. showed a similar sensitivity (93%) and a higher specificity (98%), this difference could be attributed to using acetyl-cholinesterase staining to enhance the accuracy. Investigators reported an accuracy rate of 95% with this technique, versus 85% with haematoxylin and eosin staining.[13,17]

The relatively delayed presentation in our setting is due to lack of proper referral systems. Khan et al. published comparable numbers with mean age at diagnosis of 3.6 months.[7] A significant number of referrals for rectal biopsy are initiated beyond the neonatal period, as 50% were referred to us between 1 and 12 months, and 10% beyond the age of one year. This situation makes suction rectal biopsy difficult to perform, as it is practicable only in neonates and small infants, and makes an admission for a strip rectal biopsy under GA necessary. It is important to note that the suction rectal biopsy device and kits are not available in all paediatric surgical centres in the developing world, and that it requires meticulous interpretation and cumulative experience of both the surgeon and the pathologist.

The most statistically significant clinical criteria for differentiating HD from IC were (a) neonatal onset of constipation, and/or moderate to severe abdominal distension, and/or vomiting; (b) male sex; (c) associated congenital anomalies, dysmorphic features and/or a family history of HD; (d) delayed meconium passage; (e) enterocolitis or significant bowel obstruction/impaction; (f) a digital rectal examination showing a tight anorectum.

Similarly radiologically the most important features to diagnose HD were (a) funnelled transition zone or a reversed rectosigmoid index (<1); (b) delayed evacuation of contrast after 24 h; and (c) absent distension of the anorectum with contrast, absent mucosal irregularities, and absent sigmoid convoluted looping.

Depending on that we generated a checklist of the above 6 clinical points, and 3 radiological points, to be used for assessment of patients referred for a rectal biopsy.

Table 4 Anorectal manometry in the studied groups.

Parameter	Idiopathic constipation (Number = 14)	Hirschsprung's disease (Number = 28)	*p* value
Not done	9 (64.3%)	26 (92.9%)	0.008
Adequate recto-anal inhibitory reflex	2 (14.3%)	0 (0%)	
Inadequate recto-anal inhibitory reflex	0 (0%)	2 (7.1%)	
Inconclusive: withholding spastic anal sphincters	3 (21.4%)	0 (0%)	

Table 5 Checklist and algorithm for presenting cases.

*If contrast enema is not done prior to assessment: rely on **6** clinical features*		
1. Neonatal onset of constipation, moderate to severe abdominal distension, and vomiting 2. Male sex 3. Associated congenital anomalies and/or dysmorphic features and/or family history of Hirschsprung's disease 4. Delayed meconium passage 5. Enterocolitis or significant bowel obstruction/ impaction 6. Digital rectal examination showing a tight anorectum	Proceed to rectal biopsy only if scored $\geqslant$3 out of the 6 clinical points	If patient scored $<$3: Start laxative and dietary management for 6 months. Re-evaluate after 6 months: May need contrast enema $\pm$ rectal biopsy if symptoms persist
*If contrast enema is done prior to referral: rely on **6** clinical features + **3** radiological features*		
7. Funnelled transition zone or a reversed rectosigmoid index 8. Delayed evacuation of contrast after 24 h 9. Absent distension of the anorectum with contrast, absent mucosal irregularities, and absent sigmoid convoluted looping	Proceed to rectal biopsy only if scored $\geqslant$ 5 out of the 9 clinical and radiological points	If patient scored $\leqslant$5: Start laxative and dietary management for 6 months. Re-evaluate after 6 months: May need rectal biopsy if symptoms persist

If the patient was referred before a contrast enema was done, we would proceed with a rectal biopsy only if the patient has at least 3 of the 6 clinical features (ideally $\geqslant$4), whereas if the patient is referred after an inconclusive contrast enema, we would proceed with a rectal biopsy, only if the patient has five of all the nine clinical and radiological points added together.

We expect a score of six or more out of nine on this scale to be almost always indicative for HD. Similarly, a score of three or less would usually be negative for HD and justifies labelling the case as functional constipation and conducting a follow up on outpatient basis, for at least 6 months.

We are currently employing this protocol (Table 5) to reduce unnecessary rectal biopsies to around 15%. This work is a necessary initial step towards building a governing guideline of our practice. We aim to report on the reliability and clinical effectiveness of this approach, after a sufficient number of cases for statistical analysis have prospectively been enrolled.

Ethical approval

This work has been conducted under supervision of the research committee of the Department of Surgery, Faculty of Medicine, Cairo University, Egypt. The patients involved provided an informed consent to the usage of their data for the purpose of this research.

Conflict of interest

We have no conflict of interest to declare.

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We dedicate this work with affection to the memory of our great mentors, Prof. Dr. Adel Lotfy, and Prof. Dr. Magdy El-Barbary, who were the founders of the specialty of paediatric surgery in Cairo University, Egypt, and would always remain beacons of wisdom, surgical talent, and good nature to lead us.

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