A Clinical Diagnostic Scoring System to Improve Early Treatment of Hirschsprung's Disease

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ABSTRACT:

BACKGROUND:

Hirschsprung's disease (HD) is a functional intestinal obstruction due to an abnormality of the enteric nervous system, most of affected patients with HD are presented during the neonatal period, but the diagnosis is still non-specific and leading to missing some patients.

THE AIM OF THE STUDY:

Is to construct a simple clinical predictor scoring system to assist early diagnosis, allow early treatment of HD and to avoid doing rectal biopsy as much as possible.

METHODS:

A prospective cohort study was done in Children Welfare Teaching Hospital from the first of January 2016 to the end of December 2017; the study included 52 patients who were admitted to the pediatric surgery department at neonatal period with suspicion of HD. Clinical variables which include (low birth weight, prematurity, family history of HD, male gender, passage of meconium over 48 hours, passage of meconium in first stimulation, feeding intolerance, vomiting, abdominal distention, constipation, diarrhea, dependence on anal stimulation or enemas and important radiological findings) were taken for diagnosis of HD. Rectal biopsy (full thickness) or segment biopsy were done for the included patients to divide them into negative and positive (HD) groups.

According to the statistical results, a new clinical scoring system was constructed and only the variables with significant correlation with the dependent variable (histopathology) were selected.

RESULTS:

Male to female ratio among HD patients was (3.7:1). The transitional zone by contrast enema; dependence on anal stimulation and constipation show accuracy of: 92%; 90%; and 90% respectively; while passage of meconium over 48 hours, male gender and diarrhea show accuracy of: 73%; 69%; and 60% respectively. The probability of the variables in the scoring system were measured by the area under (ROC) curve on which constipation, transitional zone by contrast enema and dependence on anal stimulation achieved 2 scores for each, while delayed passage of meconium; diarrhea and male gender achieved 1 score for each. The developed scoring system designed as 9 points, at the cut-off point (4), the score achieves sensitivity; specificity and accuracy of: 93.9%; 100%; and 96% respectively.

CONCLUSION AND RECOMMENDATION:

A developed clinical scoring system is simple and easily applied, and it is useful tool in the early diagnosis and treatment of HD by allowing a single stage pull through operation in small infants. Rectal biopsy is spared for those patients with ≤ 4 scores who are still suffering in the follow up period.

KEY WORDS: Hirschsprung's disease, scoring system.

INTRODUCTION:

HD is a functional intestinal obstruction due to abnormality of the enteric nervous system [(1)]. Abdominal distension, bilious vomiting and feeding intolerance are the clinical features that affect most of patients with HD during the neonatal period. Ninety percent of neonates presented with passage of meconium over 48 hours. Occasionally perforation in the cecum or appendix may be the first presenting problem.

Hirschsprung-associated Enterocolitis occurs in about 10% of neonates with HD [(2)].

The radiographic studies, anorectal manometry, and rectal biopsy are the appropriate diagnostic methods of HD, although it may vary according to

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age of the patients and the presenting clinical pictures [2, 3]. Dilated bowel loops [2.4] and absence gas in the rectum on a plain erect abdominal X-Ray carried high suspicion of HD and sometimes air-fluid levels [4]. For neonate with HD, the first step in the diagnostic pathway is water soluble contrast enema, on which a transition zone between the normal dilated bowel and aganglionic constricted segment is diagnostic finding [5], in addition to retention of contrast on a 24-hour post evacuation X-ray film [2, 3]. Contrast enema is useful in measuring the length of the aganglionic segment [5]. Anorectal manometry is the second tool for the diagnosis of HD depending on the absence of recto-anal inhibitory reflex which is present in normal individuals. Anorectal manometry is not accessible for neonates and it depends on skills of technician [3]. Rectal biopsy is pathognomonic for definitive diagnosis of HD, in which the absence of ganglion cells with hypertrophied nerve fibers are visualized by (Hematoxylin & Eosin) staining[2,3,6]. Acetylcholinesterase staining and calretinin immunostaining may be helpful in making the diagnosis [7, 8]. Rectal biopsy is day case clinic procedure but is not without complications such as rectal bleeding, perforation, fibrosis, and sepsis. Failure rate of rectal biopsy is (13%-22%) [9, 10, 11] in different literatures. False–negative results can occur with total colonic aganglionosis, ultra-short segment HD and if rectal biopsy was done during the first week of life [12].

At 2006, Weihong Guo et al [13] constructed a scoring system of HD in the neonatal period, this study was done in China, on 131 patients suspected to be HD by analysis of symptoms: (passage of meconium over 48 hr., vomiting, diarrhea, abdominal distention and tight anus on examination) and investigations like barium enema (transitional zone) and anorectal manometry, and then compare the results with the histopathological results. The scoring system was designed as 6 points, on which one score was given for each: passage of meconium over 48 hours and tight anus and 2 scores were given for each: barium enema and anorectal manometry. They concluded that the use of HD scoring system in the neonatal period may help in early diagnosis of HD and rectal biopsy is spared for selected patient [13].

AIM OF THE STUDY:

Is to reconstruct a clinical scoring system that assists in early diagnosis and treatment of Hirschsprung's disease by allowing single stage pull through operation and avoid rectal biopsy as much as possible.

PATIENT AND METHODS:

A prospective Cohort study was done from Jan. 2016 to Dec. 2017 in Children Welfare Teaching Hospital, department of pediatric surgery. The study included 52 patients, all of them presented at the neonatal period with suspicion of HD. This study excludes patients who are presented with perforated viscous, anorectal malformation, other neonatal intestinal obstruction and patients with suspicion of HD who are presented beyond neonatal period.

All patients were admitted to the surgical ward, and the data were recorded in a data sheet which include; name, family phone no., case sheet no., age, weight at presentation, gender, gestational age, family history of the similar condition and symptoms and signs at presentation which include: passage of meconium over 48 hours, vomiting, abdominal distention, diarrhea, constipation and feeding intolerance.

On admission to the surgical ward, resuscitation was done to all patients in an incubator by intravenous fluids, antibiotics and nasogastric tube insertion. Rectal stimulation was performed that results in failure to pass meconium or passage of mucus, meconium or pellet. Plain abdominal x-ray on erect position was done and the findings were recorded. Patients were kept on anal stimulation every 2-3 hours, and then the frequency of stimulation is reduced to be on need. When distention of abdomen is subsided and the patient tolerates feeding, discharge from hospital was done and the family instructed to bring the patient to the outpatient clinic for follow up after 4 weeks or to come at any time if the condition was deteriorated during waiting period. Dependence on rectal stimulation and irrigation was recorded during that period of time.

If the patient's condition is stable at one month old, water soluble contrast enema was requested for diagnosis of HD and the results were interpreted accordingly.

A full thickness rectal biopsy or segment biopsy were done for the included patients to confirm the diagnosis of HD and used to evaluate the scoring system variables, and these patients

were followed up for at least 6 months. By using Hematoxylin & Eosin stain by the histopathologist, an absence of ganglion cells and presence of nerves fibers hypertrophy were recorded and considered as positive histopathology for HD, while presence of ganglion cells and absence of nerve hypertrophy was considered as negative histopathology for HD.

Data analysis:

The patients who had symptoms and signs resembling HD with positive histopathology are considered as a positive group for HD. The other group is considered as a negative group depending on the presence of negative histopathology.

According to the clinical variables that include (low birth weight, prematurity, family history of HD, male gender, passage of meconium over 48 hours, passage of meconium in first stimulation, feeding intolerance, vomiting, abdominal distention, constipation, diarrhea, dependence on anal stimulation or enemas and important radiological findings (dilated bowel loops, air-fluid levels and absence gas in the rectum on a plain erect abdominal X-Ray and the presence of transitional zone in contrast enema), a clinical scoring system was reconstructed according to the statistical results, and only the variables with significant correlation with the dependent variable (histopathology) were selected to design a scoring system, and then the results of the scoring system were compared with the results of histopathology to evaluate accuracy of this scoring system.

Statistical analysis: Each patient assigned a serial number. Statistical Package for Social Sciences (SPSS) version 22 was used to analyze the data.

- Continuous data represented by mean and range.
-The categorical data were presented as frequency and percentage tables.
-The Chi-square test was used to assess the association between variables.
-Pearson test was used to assess the correlation between each variable and the dependent variable, and then only the variables with significant correlation are used in the scoring system design.
-Reliability tests (sensitivity, specificity, positive predictive value, negative predictive value, and accuracy) were calculated.
-The scores that were given to each variable in the scoring system were calculated by: Area under the receiver operating characteristic (ROC) curve of each variable multiplied by 2 and the results proximate to the integral number to easy calculation.
-The (P) Value less than 0.05 was used as significant value.
-The cutoff score for predicting HD was considered using (ROC) analysis.
-The accuracy of the score was calculated by the area under the (ROC) curve.

RESULTS:

Male to female ratio among the Positive group was 3.7:1, comparing to 0.9:1 among the Negative group. The variables with significant correlation (p-value < 0.05) were selected to design the scoring system are the following: male gender, passage of meconium over 48 hours, constipation, dependence on anal stimulation, diarrhea and transitional zone by contrast enema, as shown in table (1).

Table 1: The correlation of different variables to the dependent variable (histopathology) and incidence of each variable in positive and negative histopathology group.

Factor	Incidence		Incidence in Negative histopathology		Incidence in Positive histopathology		Correlation* and P value**	
	No.	%	No.	%	No.	%		
Low birth weight	3	5.8%	0	0.0%	3	15.8%	-.326 P: 0.018	
Prematurity	2	3.8%	0	0.0%	2	10.5%	-.264 P: 0.059	
Family history of HD	0	0.0%	0	0.0%	0	0.0%	Constant***	
Male gender	35	67.3%	26	78.8%	9	47.4%	0.323 P: 0.02	
Feeding intolerance	50	96.2%	31	93.9%	19	100%	-.152 P: 0.283	
Vomiting	42	80.8%	25	75.8%	17	89.5%	-.168 P: 0.235	
Abdominal Distention	47	90.4%	30	90.9%	17	89.5%	0.023 P: 0.869	
Passing meconium over 48 hours	47	90.4%	33	100%	14	73.6%	0.430 P: 0.001	
Constipation	36	69.2%	32	97.0%	4	21.0%	0.792 P: < 0.001	
Dependence on anal stimulation	28	53.8%	28	84.8%	0	0.0%	0.852 P: < 0.001	
Diarrhea	14	26.9%	13	39.4%	1	5.3%	0.371 P: 0.007	
Passing meconium by stimulation	52	100%	33	100%	19	100%	Constant	
Dilated bowel loop and absent gas in the rectum Plain x-ray	52	100%	33	100%	19	100%	Constant	
%Transitional zone by contrast enema	29	55.8%	29	87.9%	0	0.0%	0.852 P: < 0.001	

*Correlation: Pearson correlation test. **P value significant < 0.05.
***Constant: the variable was same in all patient.

Table (2) summarized the 6 parameters and their accuracy, on which the transitional zone by contrast enema, dependence on anal stimulation and constipation show accuracy of: 92%, 90% and 90% respectively and passage of meconium over 48 hours, male gender and diarrhea show accuracy of: 73%, 69% and 60% respectively.

Table 2: Reliability and accuracy of scoring system parameters.

Factor	Sensitivity	Specificity	PPV*	NPV**	Accuracy
Transitional zone by Contrast enema	87.9%	100.0%	100.0 %	82.6%	92%
Dependence on anal stimulation	84.8%	100.0%	100.0 %	79.2%	90%
Constipation	97%	78.9%	88.9%	93.8%	90%
Passing meconium over 48 hours	100.0%	26.3%	70.2%	100.0%	73%
Male gender	78.8%	52.6%	74.3%	58.8%	69%
Diarrhea	39.4%	94.7%	92.9%	47.4%	60%
*PPV: positive predictive value, **NPV: negative predictive value					

The probability of the variables in the clinical scoring system were calculated by the area under the receiver operating characteristic (ROC) curve, the score value derived from multiplying the (AUC) by 2 and proximate the result to the integral number to easy calculation on which: constipation, transitional zone by contrast enema and dependence on anal stimulation achieved: 2 scores for each, while passing meconium over 48 hours, diarrhea and male gender achieved: 1 score. This clinical scoring system is shown in table (3).

Table 3: The Clinical Scoring System.

Factor	Probability (AUC)	Scores
Transitional zone by CE	0.939	2
Dependence on anal stimulation	0.924	2
Constipation	0.880	2
Diarrhea	0.671	1
Male gender	0.657	1
Passing meconium over 48 hours	0.632	1

The area under the ROC curve of the diagnostic score was 0.995 (p-value < 0.001) with (95 % confidence interval, 0.984–1.000). The sum of scores of the scoring system were 9, by cut-off point 4, the score achieves sensitivity, specificity and accuracy of 93.9%, 100% and 96% respectively. Patients can be divided into two groups: group (A) patients achieved > 4 points are considered as having the disease and need to be treated surgically, and group (B) patients achieved ≤ 4 points are considered as not having the disease and rectal biopsy was undertaken for definitive diagnosis and to evaluate the scoring system variables.

There are two patients achieves (4) scores, but the Histopathology was positive for HD and so were considered as a false negative, as shown in table (4).

Table 4: The validity of the Clinical Score System.

		Histopathology		Total
		Negative	Positive	
Group	A ≤ 4	19	2	21
	B > 4	0	31	31
Total		19	33	52
Chi-Square 44.2 df 1 p value < 0.001				

Rectal biopsy had been done to 29 patients from the total number of the patients in this study, with 2 complications which are: 2 patients need re-do (because of too low and an inadequate tissue). The other 23 patients, 11 of them had been underwent primary transanal pull through with frozen biopsy while the other 12 patients had obstructive symptoms or Enterocolitis that need colostomy with segmental biopsy.

Discussion: Although most of patients with aganglionosis are presented during the neonatal period, but the diagnosis is still non-specific and leading to missing some patients. In the current study, the significant clinical variables in the diagnosis of HD were male gender, delayed passage of meconium; constipation; diarrhea; dependence on anal stimulation and the presence of the transitional zone by contrast enema.

The incidence of male to female ratio among HD patients was 3.7:1 which coincides with Suita et al [14] and Camillel Stewart [15] who found male predominance in their studies also. Delayed Passage of meconium was found in all the 33 patients of HD (100%) in this study, while Weihong Guo et al [13], Nicola A Lewis et al [16], and WuXJ et al [17] found 88%, 65% and 56% respectively in their studies. This difference between this series and others [16, 17] might be because the later series are retrospective and their data were not available in all patients. History of constipation since neonatal period was found in (36/52) patients, thirty-two out of 33 (97%) of them had HD in this study, this is similar to R. Khan et al [18] who found 92% of HD patients had onset of constipation during neonatal period. History of diarrhea and enterocolitis was found in (13/33) 39% of patients of HD in the current study, which is similar to Ghosh et al [19] who found history of enterocolitis in 47% of their patients, but it is higher than Nicola A. lewis et al [16] and lower than Weihong Guo et al [13] who found incidence of enterocolitis is of 13% and 86% respectively. The presence of the transitional zone by contrast enema was seen in (29/33) 87.8% of HD patients which is similar to others [16, 17, and 13] who found results of 80%, 83% and 90% respectively in their studies.

Although the rectal biopsy is a pathognomonic in the definitive diagnosis of HD, but it is invasive method of diagnosis and not without serious complications [9, 10, and 11]. In this study and under general anesthesia, full thickness rectal biopsy was done in 29 of patients with 2 complications which are: 2 re-do biopsies (one inadequate tissue and the other one was low biopsy), these results agree with N. K. Alizai et al [9] who took 258 infants and children in his series, they underwent rectal biopsy to exclude HD and related disorders, the complications were: (two patients rectal bleeding, one patient perforation and develop sepsis) and 27 patients were inadequate tissue.

The use of clinical scoring system in neonatal period allows single stage pull through operation in small infants and avoiding unnecessary rectal biopsy under general anesthesia. In 2006, Weihong Guo et al [13] developed a diagnostic scoring system of HD for neonatal period using 4 parameters and gave 1 score for each: delayed passage of meconium and tight anus and 2 scores were given for each: barium enema and anorectal manometry. In the present study, the former clinical scoring system can't be applicable as digital rectal examination is not preferable in the first month of life and it is a subjective sign and the anorectal manometry is not accessible for the neonates as movement and crying may interfere with the results and it depends on skills of technician.

According to different clinical variables, a new clinical scoring system was constructed depending on the statistical results and only the variables with significant correlation with the dependent variable (histopathology) were selected to design a scoring system and then the results of the scoring system were compared with results of the histopathology to evaluate the accuracy of this scoring system. This scoring system had achieved 93.9% sensitivity, 100% specificity and 96% accuracy in predicting HD at cut-off point (4)

CONCLUSION AND RECOMMENDATION:

A developed clinical scoring system is simple and easily applied, and it is useful tool in the early diagnosis and treatment of HD by allowing a single stage pull through operation in small infants. Rectal biopsy is spared for those patients with ≤ 4 scores who are still suffering in the follow up period.

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