

Risk Factors of Enterostomy in Neonates With Hirschsprung Disease

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Abstract

Purpose

To explore the risk factors of enterostomy in neonates with Hirschsprung disease (HD) to provide reference for clinicians to make treatment decisions.

Methods

The medical records of 284 patients who were diagnosed with HD during the neonatal period were retrospectively analyzed. The patients were retrospectively divided into 2 groups according to whether or not they had an enterostomy before radical surgery. Univariate and multivariable logistic regression analysis were performed to identify risk factors of enterostomy.

Results

The incidence of enterostomy was 18.5% (34/284) in neonates with HD. Univariate and multivariate logistic regression analysis showed that serum albumin < 25.4 g/L, radiographic results as subphrenic free air and level of aganglionosis with long-segment or total colonic aganglionosis (TCA) were independent risk factors of enterostomy in neonates, with OR of 42.045 (6.131, 288.319), 285.558 (26.651, 3059.694) and 15.573 (4.319, 56.157), respectively.

Conclusions

The low serum albumin level, bowel perforation and level of aganglionosis with long-segment or TCA could influence the occurrence of enterostomy in neonates with HD.

Introduction

Hirschsprung disease (HD) is a congenital bowel disorder characterized by the absence of intrinsic parasympathetic ganglia of the intestinal tract with an incidence of 1:5000[1]. Neonates commonly present with delayed passage of meconium, abdominal distention, and vomiting due to functional intestinal obstruction[2]. The previous treatments were preventive enterostomy, followed by radical operation of HD[3]. In recent years, most pediatric surgeons have accepted single stage surgery for treatment of HD, which can shorten the length of hospital stay, reduce the number of anesthesia, reduce the cost, and avoid a series of complications of enterostomy compared with multi-stage surgery[4, 5]. However, there are still a few patients with HD who need staged surgery. It is considered that for HD patients with poor preoperative colonic enema effect, complicated with severe enterocolitis, and bowel perforation, a stoma should be performed to relieve the condition[6], especially in the neonatal period, the

condition of whom is complex and volatile, which need pediatric surgeons to make a correct treatment decision quickly. Therefore, a study of risk factors for enterostomy in neonates with HD is warranted.

There are few studies focus on the risk factors of enterostomy in neonates with HD, so this study retrospectively reviewed neonates with HD diagnosed with HD in our hospital, to explore the relevant risk factors of enterostomy.

Methods

Patients and clinical characteristics

We retrospectively collected the medical records of all patients with HD, who had been diagnosed with HD in the neonatal period, admitted to the Beijing Children's Hospital between January 1, 2007 and October 1, 2021. The criteria for inclusion in the study were as follows: (1) ≤ 28 days old at the time of diagnosis of HD, (2) preoperative diagnosis of HD based on the results of suction rectal biopsy (SRB). The exclusion criteria were as follows: (1) postoperative histological findings did not support diagnosis of HD, or (2) > 28 days old at the time of diagnosis of HD.

Patient demographics, clinical presentations, laboratory values and radiographic results were collected and analyzed. The patients were retrospectively divided into 2 groups according to whether or not they had an enterostomy before radical surgery. The study was approved by the Medical Ethics Committee of Beijing Children's Hospital (2020-Z-082), and the patient informed consent requirements were waived.

Statistical analysis

Statistical analysis was performed by SPSS 26.0. Continuous variables were presented as the mean and standard deviation for normal distribution, or median and interquartile range (IQR) for non-normal distribution. Categorical variables were reported as counts and percentages. Pearson's χ^2 test, Fisher's exact test, two independent samples t -tests and the non-parametric Mann-Whitney U test was used to compare characteristics between the enterostomy and non-enterostomy groups. Receiver operating characteristic (ROC) curve analysis was performed to determine the most appropriate cut-off values. Univariate and multivariable logistic regression analysis were performed to identify risk factors of enterostomy. $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 284 cases of HD were included in this study, including 233 males (82.0%) and 51 females (18.0%), only 9 premature infants (3.2%). These patients had a median birth weight of 3450 g (range: 1560–4600 g). 39 patients (13.7%) were found to have congenital diseases, including nonsyndromic anomalies ($n = 37$), Waardenberg syndrome ($n = 1$), and Down syndrome ($n = 1$). 10 patients (3.5%) had a

specific family history of HD. Presenting symptoms included abdominal distention (272, 95.8%), vomiting (n = 215, 75.7%), delayed meconium discharge (n = 246, 86.6%), feeding intolerance (n = 85, 29.9%), diarrhea (n = 24, 8.5%), and fever (n = 39, 13.7%). Fifteen patients (5.3%) showed free air under the diaphragm on abdominal plain radiographs, and bowel perforation was confirmed intraoperatively in the ileum (1/15, 6.7%), ileocecum (1/15, 6.7%), ascending colon (2/15, 13.3%), transverse colon (1/15, 6.7%), descending colon (2/15, 13.3%), and sigmoid colon (8/15, 53.3%).

In total, 235 neonates (82.7%) with HD undergone one-stage transanal endorectal pull-through (TEPT) with a median age at surgery of 17 days (range: 2–28 days); 15 neonates (5.3%) who were diagnosed with HD by clinical manifestations and SRB had been managed with colon enema in the early stage, and then, they received one-stage TEPT, at a median age of 118 days (range: 41–202 days); 34 neonates (12.0%) with HD received enterostomy including ileostomy (14/34, 41.2%) and colostomy (20/34, 58.8%) prior to definitive surgery. The level of aganglionosis was determined to be short-segment (197, 69.4%), long-segment (71, 25.0%), and total colonic aganglionosis (TCA) (16, 5.6%).

Comparison of clinical characteristics between the enterostomy and non-enterostomy groups

Of the 284 neonates in this group, enterostomy was performed in 34 cases (12.0%). As shown in Table 1, by comparing clinical characteristics between enterostomy (n = 34) and non-enterostomy groups (n = 250), we found significant differences in fever, preoperative mechanical ventilation, level of aganglionosis, C-reactive protein (CRP), neutrophil ratio (NEUT%), plasma albumin, plasma fibrinogen (FIB), radiographic results as subphrenic free air, and radiographic results as intestinal wall pneumatosis (all $p < 0.05$). There were no differences between the two groups for other clinical characteristics (all $p > 0.05$).

Table 1
Comparison between enterostomy and non-enterostomy groups

Variables		Enterostomy (n = 34)	Non- enterostomy (n = 250)	Results	<i>p</i>
Sex (n, %)	Male	28 (82.4)	205 (82.0)	0.003	0.960
	Female	6 (17.6)	45 (18.0)		
Gestational age (n, %)	Preterm	3 (8.8)	6 (2.4)	2.185	0.139
	Term	31 (91.2)	244 (97.6)		
Maternal age (mean ± SD, y)		30.3 ± 5.6	28.7 ± 4.6	1.645	0.101
Birth weight (median, IQR, g)		3510.0 (3000.0, 3800.0)	3450.0 (3115.0, 3700.0)	-0.775	0.438
Hospital weight (median, IQR, g)		3380.0 (3045.0, 3620.0)	3330.0 (3080.0, 3600.0)	-0.045	0.964
Subtraction of birth weight from hospital weight (mean ± SD, g)		-150.0 (-300.0, 20.0)	-10.0 (-232.5, 82.50)	-1.569	0.117
Age at admission (median, IQR, day)		4.0 (3.0, 16.0)	5.0 (3.0, 10.0)	-0.553	0.580
Clinical presentations					
Abdominal distention (n, %)	Yes	33 (97.1)	239 (95.6)	0.157	0.692
	No	1 (2.9)	11 (4.4)		
Vomiting (n, %)	Yes	29 (85.3)	186 (74.4)	1.931	0.165
	No	5 (14.7)	64 (25.6)		
Diarrhea (n, %)	Yes	4 (11.8.0)	20 (8.0)	0.170	0.680
	No	30 (88.2)	230 (92.0)		
Delayed meconium Discharge (n, %)	Yes	30 (88.2.3)	216 (86.4)	0.001	0.979
	No	4 (11.8)	34 (13.6)		
Feeding intolerance (n, %)	Yes	12 (35.3)	73 (29.2)	0.530	0.467

Abbreviations: WBC, white blood cell count; PLT, platelet count; RBC, red blood cell count; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate amino transferase; ALT, alanine aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; PT, prothrombin time; APTT, activated partial thromboplastin time.

Variables		Enterostomy (n = 34)	Non- enterostomy (n = 250)	Results	<i>p</i>
	No	22 (64.7)	177 (70.8)		
Fever (n, %)	Yes	9 (26.5)	30 (12.0)	4.139	0.042
	No	25 (73.5)	220 (88.0)		
Dehydration (n, %)	Yes	4 (11.8)	11 (4.4)	1.940	0.164
	No	30 (88.2)	239 (95.6)		
Pneumonia (n, %)	Yes	7 (20.6)	46 (18.4)	0.094	0.759
	No	27 (79.4)	204 (81.6)		
Heart rate (median, IQR, /min)		136.0 (132.0, 150.0)	139.0 (130.0, 150.0)	-0.677	0.498
Respiratory rate (median, IQR, /min)		36.0 (30.0, 40.0)	36.0 (32.0, 43.0)	-0.677	0.449
Preoperative mechanical ventilation (n, %)	Yes	5 (14.7)	1	16.725	< 0.001
	No	29 (85.3)	249 (99.6)		
Associated anomalies (n, %)	Yes	6 (17.6)	33 (13.2)	0.195	0.659
	No	28 (82.4)	217 (86.8)		
Family history (n, %)	Yes	1 (2.9)	9 (3.6)	0.038	0.845
	No	33 (97.1)	241 (96.4)		
Level of aganglionosis (n, %)	Long-segment /TCA	26 (76.5)	62 (24.8)	37.367	< 0.001
	Short-segment	8 (23.5)	188 (75.2)		
Laboratory values					
CRP (n, %)	> 8 mg/L	21 (61.8)	43 (17.2)	34.050	< 0.001
	≤ 8 mg/L	13 (38.2)	207 (82.8)		

Abbreviations: WBC, white blood cell count; PLT, platelet count; RBC, red blood cell count; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate amino transferase; ALT, alanine aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; PT, prothrombin time; APTT, activated partial thromboplastin time.

Variables		Enterostomy (n = 34)	Non- enterostomy (n = 250)	Results	<i>p</i>
WBC (median, IQR ×10 ⁹ /L)		9.34 (4.7, 19.4)	12.0 (9.2, 15.7)	-1.389	0.165
NEUT% (median, IQR)		65.3 (46.1, 73.3)	46.0 (35.5, 63.9)	-3.261	0.001
PLT (mean ± SD, ×10 ⁹ /L)		295.8 ± 108.4	315.7 ± 137.3	-0.707	0.481
RBC (median, IQR ×10 ¹² /L)		4.6 (3.9, 5.6)	4.8 (4.3, 5.5)	-0.757	0.449
Hemoglobin (median, IQR, g/L)		159.6 ± 39.5	167.6 ± 35.9	-1.155	0.249
Serum albumin (median, IQR, g/L)		33.9 (25.8, 36.3)	35.2 (32.5, 38.4)	-2.092	0.036
BUN (median, IQR, mmol/L)		5.3 (4.2, 7.5)	4.2 (2.7, 7.1)	-1.252	0.211
Serum creatinine (median, IQR, μm/L)		41.7 (25.2, 62.3)	37.9 (26.4, 60.6)	-0.120	0.904
ALP (median, IQR, U/L)		119.0 (71.3, 148.3)	129.0 (100.0, 164.8)	-1.697	0.090
AST (median, IQR, U/L)		38.3 (29.5, 47.9)	41.0 (32.0, 59.5)	-1.454	0.146
ALT (median, IQR, U/L)		11.4 (8.7, 16.2)	13.0 (9.8, 18.8)	-1.169	0.242
TBIL median, IQR, μm/L)		143.1 (41.1, 172.3)	134.1 (76.4, 194.8)	-0.965	0.335
DBIL (median, IQR, μm/L)		8.6 (5.2, 13.2)	7.2 (5.1, 10.0)	-1.442	0.149
PT (median, IQR, sec)		12.9 (11.3, 16.6)	12.8 (11.9, 14.4)	-0.067	0.947
APTT (median, IQR, sec)		47.3 (40.5, 57.6)	48.1 (42.2, 56.5)	-0.016	0.987
Fibrinogen (median, IQR, g/L)		2.8 (2.1, 3.1)	2.0 (1.7, 2.4)	-3.364	0.001
Radiographic results					
Subphrenic free air (n, %)	Yes	14 (41.2)	1 (0.4)	91.491	< 0.001

Abbreviations: WBC, white blood cell count; PLT, platelet count; RBC, red blood cell count; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate amino transferase; ALT, alanine aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; PT, prothrombin time; APTT, activated partial thromboplastin time.

Variables		Enterostomy (n = 34)	Non-enterostomy (n = 250)	Results	p
	No	20 (58.8)	249 (99.6)		
Gas-fluid level (n, %)	Yes	12 (35.3)	75 (30.0)	0.395	0.530
	No	22 (64.7)	175 (70.0)		
Intestinal wall pneumatosis (n, %)	Yes	5 (14.7)	8 (3.2)	6.682	0.010
	No	29 (85.3)	242 (96.8)		
Abbreviations: WBC, white blood cell count; PLT, platelet count; RBC, red blood cell count; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate amino transferase; ALT, alanine aminotransferase; TBIL, total bilirubin; DBIL, direct bilirubin; PT, prothrombin time; APTT, activated partial thromboplastin time.					

Risk factors of enterostomy

In order to find the risk factors of enterostomy in neonates with HD, we conducted a multivariate analysis. ROC curve analysis was used to determine the stratification value for NEUT%, plasma albumin and FIB according to the maximum combined sensitivity and specificity values, and the cut-off values for the above characteristics were 44.4, 25.4 g/L and 2.4 g/L, respectively. As shown in Table 2, multivariate analysis showed that serum albumin < 25.4 g/L, radiographic results as subphrenic free air and level of aganglionosis with long-segment or TCA were independent risk factors of enterostomy in neonates with HD, with OR of 42.045 (6.131, 288.319), 285.558 (26.651, 3059.694) and 15.573 (4.319, 56.157), respectively.

Table 2
Multivariate logistic regression analysis of enterostomy

Variables	Estimate	Standard Error	Wald	P	OR
Serum albumin < 25.4 g/L	3.739	0.982	14.486	< 0.001	42.045 (6.131, 288.319)
Subphrenic free air	5.654	1.210	21.837	< 0.001	285.558 (26.651, 3059.694)
Long-segment/TCA	2.746	0.654	17.603	< 0.001	15.573 (4.319, 56.157)

Discussion

Most HD children are diagnosed and treated in the neonatal period and early infancy, and the main treatment principle of HD is resection of the diseased bowel segment[7]. Despite the fact that one-stage operation has become preferred practice in managing HD, some children require an enterostomy in neonatal period. Patients undergoing stage surgery had higher rates of readmissions and additional operations[4], therefore, to make the appropriate treatment decisions, it's essential to understand the factors that influence enterostomy. According to literature reports, the incidence of enterostomy in infants with HD is 15.4% – 53%, and presents a gradually decreasing trend[4, 8–10]. In our study, the incidence of enterostomy was 12.0%, which was relatively lower.

Few studies have reported the influencing factors of enterostomy. According to a retrospective United States analysis of a multi-institutional cohort of neonates with HD, showed that patients with low birth weights, premature delivery, and non-HD gastrointestinal anomalies were more likely to undergo a stoma before definite surgery[4]. Previous studies showed that Down syndrome was strongly associated with stoma formation[8, 11]. In this study, the factors mentioned above were not independently related to the enterostomy, and we found that low serum albumin level, bowel perforation and level of aganglionosis with long-segment and TCA were significant independent risk factors of enterostomy in neonatal HD patients.

We found that the serum albumin level was significantly lower of patients with stoma than that of patients without stoma. The serum albumin was usually used to assess acute versus chronic malnutrition, but some studies showed it was likely more predictive of inflammation and morbidity rather than nutritional status[12, 13]. In our study, there was no significant difference in birth weight or hospital weight between the enterostomy group and the non-enterostomy group, but there were significant differences in many inflammation-related indexes such as CRP, WBC, NEUT% between the two groups, which seemed to indicate that the decrease of albumin was related to the poor state of the patient.

Commonly reported factors influencing the decision for enterostomy include the presence of preoperative enterocolitis[9, 14, 15]. However, Bradnock et al.[8] indicated that enterocolitis were not independently correlated with stoma formation. This could be because the clinical definition of enterocolitis is still elusive, making it difficult to capture the case. We did not collect cases of enterocolitis, but we collected and analyzed clinical factors associated with the diagnosis of enterocolitis[16], such as diarrhea, distended abdomen, fever, CRP, WBC, NEUT%, radiographic results as gas-fluid level, and radiographic results as intestinal wall pneumatosis. The results showed that fever, CRP, NEUT%, and radiographic results were associated with enterostomy, but they were not significant in multivariate logistic regression analysis, possibly due to they were predictors of enterocolitis that might lead to enterostomy. Since previous studies have used different definitions of HD associated enterocolitis, factors for the relationship between enterocolitis and enterostomy are not absolute, and the conclusions are still controversial.

According to European Reference Network for Rare Inherited Congenital Anomalies (ERNICA) guidelines for the management of rectosigmoid HD, a stoma is indicated if there is bowel perforation[6]. In our study,

the incidence of bowel perforation was 5.3%, and the multivariate logistic regression analysis showed that radiographic results as subphrenic free air was a vital risk factor of enterostomy. Although most HD patients mainly present with low intestinal obstruction in the neonatal period, there are also some children with intestinal perforation as the first symptom, mostly located in the cecum and appendix[1]. However, we found that 53.3% of patients (8/15) had perforations in the sigmoid colon, which was similar to another research about perforated HD[17]. The intestines of newborns with HD associated enterocolitis are very fragile and easy to perforate during colon enema. In this group, 4 cases had obvious abdominal distension on admission, which could not be relieved by diet resistance, and received colon enema. Unfortunately, the 4 patients developed intestinal perforation after colon enema. Therefore, for institutions with less experience in colon enema in the neonatal period, in order to avoid iatrogenic perforation and aggravation of the patient's condition, temporary enterostomy could be selected. The atypical manifestations of neonatal intestinal perforation make clinical diagnosis and treatment extremely difficult. Once a diagnosis has been made, an exploratory laparotomy should be performed as soon as possible, and pathological biopsy should be performed during the operation on children suspected of HD[18].

In addition, two patients needed preoperative mechanical, and both had bowel perforation. we found preoperative mechanical was associated with enterostomy, consistent with the previous study[4], which might mean that patients was seriously ill and needed emergency surgery. However, the number of events in this study was limited, necessitating additional research.

Compared to rectosigmoid HD, long-segment HD or TCA conferred a higher rate of stoma formation[9, 15, 19]. In this study, type of HD with long-segment and TCA was an independent risk factor in multivariate logistic regression analysis, which was in agreement with a prospective study[8]. The intestinal obstruction in children with long-segment or TCA often appeared earlier, and the effect of colon enema was poor, which was easy to complicated with enterocolitis[20]. As a result, if neonates with long-segment HD or TCA are in poor general condition, an enterostomy may be preferable. It is worth mentioning that not all long-segment HD require functioning stoma in the neonatal period, which is also reflected in our data.

The retrospective nature of this study limited it, and it was subjected to several confounding variables such as variation in the preoperative management protocol over the study period. Although some of the analyses in this study did not reach statistical significance, we believe they may be clinically important, and these risk factors should be closely monitored. Additionally, cases of HD that were treated on an outpatient basis during neonatal period would not be captured in our cohort. A prospective study is required to explore the relationship between additional risk factors and enterostomy.

Conclusions

In conclusion, temporary enterostomy is an important means to relieve the condition of HD patients with low serum albumin level, intestinal perforation, and long-segment HD or even TCA suggested by

preoperative examination during the neonatal period.

Declarations

Author Contributions

Jinshi Huang, Yanan Zhang, and Zhaozhou Liu designed the study. Zhaozhou Liu and Yanan Zhang wrote the main manuscript text. Yongwei Chen, Weihong Guo, Dawei Hou, and Yingzi Li prepared table 1-2. All authors reviewed the manuscript.

Conflict of interest

The authors declare no competing interest.

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