

INFLUENCE FACTORS OF ENTEROCOLITIS RISK IN INFANTS WITH HIRSCHSPRUNG' S DISEASE AFTER SURGICAL RESECTION

JINHUI LIN¹, JIANG WU^{2,*}, ZHIBO QU¹, JIANHUA ZHONG¹, YINGSONG LIU¹, DA MAI, QINFANG XU¹, YI WANG¹

¹Department of Pediatric Surgery, Dongguan Children's Hospital Affiliated to Guangdong Medical University, Dongguan, 523325, Guangdong, P R China - ²Department of Pediatric Surgery, Affiliated Hospital of Guangdong Medical University, Zhanjiang, 524000, Guangdong, PR China

ABSTRACT

Introduction: To investigate the influence factors of enterocolitis (EC) risk in infants with Hirschsprung's disease after surgical resection.

Materials and methods: 109 infants with Hirschsprung's disease after surgical resection who underwent pediatric surgical resection from January 2015 to December 2021 were included retrospectively, including 30 cases of postoperative EC. The baseline clinical characteristics of EC and non-EC groups were compared, and independent risk factors for postoperative EC were evaluated using a Logistic Regression model.

Results: There was no significant difference between 2 groups in age and gender ($P>0.05$). There were statistically significant differences in the proportions of preoperative intestinal lavage time $\leq 14d$, preoperative malnutrition, preoperative EC, intestinal flora disorder, dietary intervention, postoperative anastomotic fistula or stenosis and intestinal obstruction between 2 groups ($P<0.05$). Logistic regression model multivariate analysis showed that preoperative malnutrition, preoperative EC, intestinal flora disorder, concurrent intestinal obstruction, preoperative intestinal lavage time $\leq 14d$, and postoperative anastomotic fistula or stenosis were all independent risk factors for postoperative EC ($P<0.05$).

Conclusion: The occurrence of EC after surgical resection in infants with Hirschsprung's disease is related to many factors. Children who have preoperative malnutrition, preoperative EC, intestinal flora disorder, concurrent intestinal obstruction, preoperative intestinal lavage time $\leq 14d$, and postoperative anastomotic fistula or stenosis are more likely to develop postoperative EC.

Keywords: Hirschsprung's disease, infant, surgery, enterocolitis.

DOI: 10.19193/0393-6384_2022_4_436

Received March 15, 2022; Accepted June 25, 2022

Introduction

Hirschsprung's disease is a common intestinal malformation in infants. It is mainly caused by persistent luminal spasm secondary to absence of intestinal ganglia and impatent intestinal canal. The affected children have delayed defecation after birth, and their intestinal contents cannot be discharged normally. If not handled in time, they can develop intractable constipation and abdominal distension, and eventually lead to megacolon changes^(1, 2). Surgical treatment is recommended for infants with

Hirschsprung's disease, but the surgical operation is complicated, and has obvious stress response. The risk of postoperative abnormal defecation and enterocolitis (EC) is high, which seriously influences the process of postoperative rehabilitation⁽³⁾. It has been reported that the incidence of EC after Hirschsprung's disease surgery can reach 20~35%, and such complications can progress to septic shock, which not only affects the recovery of physiological function, but also threatens life⁽⁴⁾. However, there is no clear conclusion as to how to identify high-risk groups of postoperative EC. Based on the

above evidence, our study analyzed the clinical characteristics of 109 infants with Hirschsprung's disease undergoing pediatric surgical treatment from January 2017 to December 2021 retrospectively, and compared the differences between EC and non-EC groups, so as to further explore the risk factors of EC after surgical resection in infants with Hirschsprung's disease, with a view to provide more reference for subsequent clinical diagnosis and treatment.

Materials and methods

General data

109 infants with Hirschsprung's disease undergoing surgical resection in Pediatric Surgery of Dongguan Children's Hospital Affiliated to Guangdong Medical University and Pediatric Surgery of Affiliated Hospital of Guangdong Medical University from January 2015 to December 2021 were included retrospectively, including 30 cases of postoperative EC.

Inclusion criteria:

- Met diagnostic criteria for Hirschsprung's disease in barium meal and histopathological examination;
- Completed transanal Soave radical surgery or laparoscopically modified Soave radical megacolecotomy;
- With complete clinical data.

Exclusion criteria:

- Malformation in other parts;
- Dysfunction of vital organs;
- Long-segmental Hirschsprung's disease;
- The surgery failed.

The research design conformed to the requirements of the Declaration of Helsinki of the World Medical Association.

Methods

Diagnostic criteria for EC

The diagnostic and grading criteria for EC were drawn from relevant literature (5): mild, the diarrhea frequency <10 times/d, the body temperature <38°C, intestinal mucosa hyperemia or mild edema can be seen endoscopically; moderate, acute diarrhea, with moderate to severe abdominal distension, higher heart rate or dehydration, the body temperature was 38~40°C, focal destruction of colonic mucosa or ulceration can be seen endoscopically; severe, explosive diarrhea, the diarrhea frequency >10 times/d, with severe abdominal distention, high

fever, shock and other symptoms. Extensive ulcer and even perforation of colonic mucosa can be seen endoscopically.

Data collection

The author logged on the electronic medical record system to collect the affected children's age, gender, preoperative treatment, surgery, nutritional status, intestinal flora, histopathological examination and postoperative complications.

Statistical processing

SPSS 19.0 software was adopted for data analysis. Kolmogorov-Smirnov test was used to evaluate normality. The measurement data conforming to normal distribution were compared by an independent sample t test and expressed by ($\bar{x}\pm s$). The enumeration data were compared by χ^2 test, and expressed by %. Logistic regression model was used to make a multivariate analysis. $P<0.05$ was considered to be statistically significant.

Results

Comparison of baseline clinical characteristics between EC and non-EC groups

There was no significant difference between 2 groups in age and gender ($P>0.05$). There were statistically significant differences in the proportions of preoperative intestinal lavage time ≤ 14 d, preoperative malnutrition, preoperative EC, intestinal flora disorder, dietary intervention, postoperative anastomotic fistula or stenosis and intestinal obstruction between 2 groups ($P<0.05$). See Table 1.

Indicators	EC Group (n=30)	Non-EC Group (n=79)	P
Age (years)	1.39±0.32	1.34±0.29	0.21
Male (cases)	22	58	0.85
Preoperative intestinal lavage time ≤ 14 d (cases)	21	20	0.00
Preoperative malnutrition (cases)	19	22	0.00
Preoperative EC (cases)	16	12	0.00
Intestinal flora disorder (cases)	22	20	0.00
Dietary intervention (cases)	28	63	0.03
Postoperative anastomotic fistula or stenosis (cases)	16	11	0.00
Intestinal obstruction (cases)	18	16	0.00

Table 1: Comparison of baseline clinical characteristics between EC group and non-EC group.

Multivariate Analysis of Logistic Regression Model of Risk Factors for postoperative EC in Affected Children

Multivariate analysis of Logistic regression model showed that preoperative malnutrition, preoperative EC, intestinal flora disorder, concurrent intestinal obstruction, preoperative intestinal lavage time ≤ 14 d and postoperative anastomotic fistula or stenosis were all independent risk factors for postoperative EC in affected children ($P < 0.05$); See Table 2.

Indicators	β	Wald χ^2	P	OR	95%CI
Preoperative malnutrition	2.03	21.83	0.00	9.27	1.81~16.14
Preoperative EC	2.67	13.57	0.00	8.86	3.70~17.98
Intestinal flora disorder	2.81	13.31	0.00	12.54	2.22~19.59
Concurrent intestinal obstruction	3.55	12.29	0.00	15.09	5.15~25.61
Preoperative intestinal lavage time ≤ 14 d	2.23	16.53	0.00	13.84	1.43~19.96
Postoperative anastomotic fistula or stenosis	2.81	19.31	0.00	10.54	2.22~20.59

Table 2: Multivariate analysis of logistic regression model of risk Factors for postoperative EC in affected children.

Discussion

EC is one of the most common complications after Hirschsprung's disease surgery. It has been reported that EC may be closely associated with the defect of intestinal mucosal barrier function and intestinal canal spasm and stenosis⁽⁶⁾. The occurrence of EC not only leads to the great loss of nutrients and body fluids of infants and young children. If not controlled in time, they may also cause acidosis, shock and even death⁽⁷⁾. Some studies have shown that the incidence of EC after Hirschsprung's disease surgery can reach 35%⁽⁸⁾. 30 of the 109 infants included in this study developed postoperative EC, with an incidence of 27.52%. Considering the high postoperative incidence, medical staff should attach importance to the rehabilitation of children with Hirschsprung's disease after surgery, identify high-risk groups as early as possible and develop more aggressive preventive interventions.

The multivariate analysis in this study verified that preoperative malnutrition, long-segmental megacolon, preoperative EC, intestinal flora disorder, intestinal obstruction, preoperative intestinal lavage time ≤ 14 days and postoperative anastomotic fistula or stenosis were all independent risk factors for postoperative EC in affected children ($P < 0.05$). Nutritional status has been proved to

directly influence the immune function of infants, and malnourished people often have poor resistance to pathogens, and the transport of poly IgA and the expression of secretory IgA can decrease in vivo. Secretory IgA is the main antibody of human mucosal immunity, which effectively inhibits pathogen adhesion and avoids damage to the integrity of the mucosal barrier^(9, 10). With the decrease of the expression of secretory IgA in the gastrointestinal tract, the probability that bacteria and viruses adhere to intestinal mucosa increases, they can multiply rapidly in large numbers, destroy the immune function of the intestinal tract and finally increase the risk of EC^(11, 12). Preoperative EC can result in chronic injury of intestinal mucosa, significant decrease of the immune function of endothelial cells and intestinal mucosal barrier. Among infants with Hirschsprung's disease, the damage of intestinal immune cells and intestinal defense system interacts with preoperative EC, while surgical stimulation can further stimulate the occurrence of postoperative EC^(13, 14). Intestinal flora disorder is considered to induce the disturbance of micro ecological balance, the damage of intestinal mucosal biological barrier, and bacteria or viruses adhere and colonize on intestinal epithelial cells in large quantities⁽¹⁵⁾. It has been reported that EC is closely related to intestinal flora disorder, and the results of this study also support this viewpoint.

However, the occurrence of intestinal obstruction can lead to the local massive accumulation of intestinal contents, pathogenic bacteria multiply rapidly and the formation of endotoxin further damage and invade intestinal mucosal tissues, destroy the barrier function of intestinal mucosa and finally raise the risk of postoperative EC in infants with Hirschsprung's disease^(16, 17). The main purpose of preoperative intestinal lavage for infants with Hirschsprung's disease is to remove feces, minimize toxin absorption and promote intestinal canal retraction. However, the lavage time often reflects the condition of the intestinal tract. The preoperative intestinal lavage time is short, and the intestinal preparation is often insufficient.

The more severe postoperative injury, the higher risk of postoperative EC^(18, 19). Anastomotic fistula or stenosis after Hirschsprung's disease surgery can cause intestinal feces to accumulate locally, and pathogens in the intestinal tract multiply, damage and invade the intestinal mucosa, and destroy the immune system, which is considered to be an important cause of postoperative EC⁽²⁰⁾. In summary, the occurrence of EC after surgical resection in infants with

Hirschsprung's disease is related to many factors. Children who have preoperative malnutrition, preoperative EC, intestinal flora disorder, concurrent intestinal obstruction, preoperative intestinal lavage time ≤ 14 d, and postoperative anastomotic fistula or stenosis are more likely to develop postoperative EC.

References

- 1) Yoshimaru K, Yanagi Y, Obata S, et al. Acetylcholinesterase staining for the pathological diagnosis of Hirschsprung's disease. *Surg Today* 2021; 51(2): 181-186.
- 2) Guillaume AWD, Miller AC, Nguyen MC. Enterocolitis in a Child with Hirschsprung Disease. *Pediatr Emerg Care*, 2019; 35(7): e131-e132.
- 3) Pruitt LCC, Skarda DE, Rollins MD, et al. Hirschsprung-associated enterocolitis in children treated at US children's hospitals. *J Pediatr Surg* 2020; 55(3): 535-540.
- 4) Keck S, Galati-Fournier V, Kym U, et al. Lack of Mucosal Cholinergic Innervation Is Associated With Increased Risk of Enterocolitis in Hirschsprung's Disease. *Cell Mol Gastroenterol Hepatol* 2021; 12(2): 507-545.
- 5) Plekhova V, De Paepe E, Van Renterghem K, et al. Disparities in the gut metabolome of post-operative Hirschsprung's disease patients. *Sci Rep* 2021; 11(1): 16167-16172.
- 6) Biassoni R, Di Marco E, Squillario M, et al. Pathways and microbiome modifications related to surgery and enterocolitis in Hirschsprung disease. *Pediatr Surg Int* 2022; 38(1): 83-98.
- 7) Lin Z, Lin Y, Bai J, et al. Outcomes of preoperative anal dilatation for Hirschsprung disease. *J Pediatr Surg* 2021; 56(3): 483-486.
- 8) Le-Nguyen A, Righini-Grunder F, Piché N, et al. Factors influencing the incidence of Hirschsprung associated enterocolitis (HAEC). *J Pediatr Surg* 2019; 54(5): 959-963.
- 9) Arafa A, Mohamed W, Taher H, et al. Laparoscopic-assisted transanal pull-through for Hirschsprung's children older than 3 years: A case series. *Afr J Paediatr Surg* 2021; 18(4): 210-214.
- 10) Arbizu R, Freiberg B, Rodriguez L. Lower Gastrointestinal Functional and Motility Disorders in Children. *Pediatr Clin North Am* 2021; 68(6): 1255-1271.
- 11) Huang WK, Li XL, Zhang J, et al. Prevalence, Risk Factors, and Prognosis of Postoperative Complications after Surgery for Hirschsprung Disease. *J Gastrointest Surg* 2018; 22(2): 335-343.
- 12) Pruitt LCC, Skarda DE, Rollins MD, et al. Hirschsprung-associated enterocolitis in children treated at US children's hospitals. *J Pediatr Surg* 2020; 55(3): 535-540.
- 13) Balakrishnan K, Perez IA, Keens TG, et al. Hirschsprung disease and other gastrointestinal motility disorders in patients with CCHS. *Eur J Pediatr* 2021; 180(2): 469-473.
- 14) Neuvonen MI, Korpela K, Kyrklund K, et al. Intestinal Microbiota in Hirschsprung Disease. *J Pediatr Gastroenterol Nutr* 2018; 67(5): 594-600.
- 15) Harrington AW, Gasior AC, Einarsdottir H, et al. Hirschsprung Disease: The Rise of Structured Transition and Long-term Care. *J Pediatr Gastroenterol Nutr* 2019; 69(3): 306-309.
- 16) Ghorbanpour M, Seyfrabie MA, Yousefi B. Early and long-term complications following transanal pull-through Soave technique in infants with Hirschsprung's disease. *Med Pharm Rep* 2019; 92(4): 382-386.
- 17) Feng X, Lacher M, Quitman J, et al. Health-Related Quality of Life and Psychosocial Morbidity in Anorectal Malformation and Hirschsprung's Disease. *Eur J Pediatr Surg* 2020 30(3): 279-286.
- 18) Nakamura H, Puri P. Concurrent Hirschsprung's disease and anorectal malformation: a systematic review. *Pediatr Surg Int* 2020; 36(1): 21-24.
- 19) Pini Prato A, Arnoldi R, Sgrò A, et al. Hirschsprung disease and Down syndrome: From the reappraisal of risk factors to the impact of surgery. *J Pediatr Surg* 2019; 54(9): 1838-1842.
- 20) Zhou L, Zhi Z, Lv X, et al. Lipopolysaccharide upregulates miR-132/212 in Hirschsprung-associated enterocolitis, facilitating pyroptosis by activating NLRP3 inflammasome via targeting Sirtuin 1 (SIRT1). *Aging (Albany NY)* 2020; 12(18): 18588-18602.

Corresponding Author:

JIANG WU

No.57, South of Renmin Avenue, Xiashan District, Zhan-jiang City, Guangdong Province, China

Email: wj2630@163.com

(China)