sciendo
10.2478/AMB-2025-0007

ORIGINAL ARTICLE

INVESTIGATING THE DIAGNOSTIC AND RISK FACTORS FOR ENTEROCOLITIS IN CHILDREN WITH HIRSCHSPRUNG'S DISEASE

S. Askarpour[1], H. Javaherizadeh[2], M. Peyvasteh[1], A. Mohammadi[3], S. Soma Seyedsalehi[3]

[1]Department of Pediatric Surgery, Children's Medical Center, Ahvaz Jundishapur University of Medical Sciences – Ahvaz, Iran
[2]Department of Pediatric Gastroenterology, Ahvaz Jundishapur University of Medical Sciences – Ahvaz, Iran
[3]Department of Surgery, Ahvaz Jundishapur University of Medical Sciences – Ahvaz, Iran

Abstract. Aim: *This study aimed to identify the clinical risk factors associated with Hirschsprung-associated enterocolitis (HAEC) in children with Hirschsprung's disease (HD).* ***Method:*** *A total of 75 children diagnosed with HD were recruited in this observational prospective study. Then, the clinical and paraclinical symptoms of children with Hirschsprung's disease (n = 57) were compared to those with HAEC (n = 18). P-value < 0.05 was considered statistically significant.* ***Results:*** *No significant difference was found between the two groups in terms of age (P = 0.72), gender (P = 0.51), and family history of HD (P = 0.25). Also, no significant difference in the rates of diarrhea (P = 0.59) and colicky pain (P = 0.99) was observed between the two groups. However, the rates of abdominal distension (P = 0.02) and lethargy (P = 0.01) were significantly higher among children with HAEC. Moreover, the incidence rates of dilated loops of bowel (P = 0.001), rectosigmoid cut-off sign (P = 0.01) and sepsis (P = 0.001) were significantly higher in the HAEC group than in patients with HD. The incidence of pneumoperitoneum was higher in HAEC patients (11.1% vs 5.3% in patients with HD), but not significantly so (P = 0.58). Moreover, no significant difference was found between the two groups in terms of leukocytosis (P = 0.46) and the incidence of short and/or long-segment colon aganglionosis (P = 0.65).* ***Conclusion:*** *Clinical symptoms of abdominal distension, dilated loops of bowel, lethargy, sepsis, and pneumoperitoneum as well as the rectosigmoid cut-off sign on the CT-scanogram may specifically indicate and differentiate HAEC in children with Hirschsprung's disease, which should be promptly diagnosed and treated.*

Key words: *hirschsprung, enterocolitis, children, risk factors*

Corresponding author: *Seyede Soma Seyedsalehi, Department of Surgery, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, e-mail: s.salehie33@ajums.ac.com*

ORCID: *0009-0005-0532-6960*

Received: *26 June 2024;* ***Revised:*** *19 August 2024,* ***Accepted:*** *13 January 2025*

INTRODUCTION

Hirschsprung's disease (HD) or congenital aganglionic megacolon is caused by the arrest of the development of the fetal myenteric nervous system (myenteric ganglion cells). Its incidence ranges from 1 per 4400 to 1 per 7000 live births, and about 70 to 80 percent of affected cases are boys [1]. This disease occurs in the distal part of the digestive tract and leads to functional obstruction of the colon and constipation. The cause of spasm in the distal part is not known, but the absence or inappropriate function of the ganglion cells, excessive cholinergic innervation of the tissue, disproportionate distribution of nitric oxide synthesis and interstitial cells of Cajal dysfunction can be possible causes of this disorder [2, 3]. In Hirschsprung's disease, the distal segment of the colon has no natural movement due to a congenital absence of parasympathetic ganglion cells. Therefore, the proximal intestine expands, which leads to functional intestinal obstruction and puts these patients at high risk of enterocolitis. Also, the sphincteric relaxation in response to rectal dilatation is disturbed, which is the basis of the diagnostic modality of anorectal manometry [4].

Most cases of HD are diagnosed in infancy. A failure to pass meconium within 48 hours after birth, vomiting and abdominal distension may be associated with Hirschsprung's disease, which should be differentiated from hypoganglionosis, neuronal intestinal dysplasia type A, hypothyroidism, hypercalcemia, hypokalemia, sepsis and congestive heart failure. In particular, the radiographic findings of HD are similar to neuronal intestinal dysplasia type A and hypoganglionosis. A history of neonatal constipation, stunted growth, abdominal distension, and empty rectal ampulla in rectal examination indicate HD in older children. Full-thickness rectal biopsy is suggested as the most reliable test to prove the diagnosis. Patients who have been diagnosed with HD undergo corrective surgery [5, 7].

Successful treatment of childrens and children with HD depends on rapid diagnosis and early treatment, and it can only be treated with surgical intervention. If the disease is not diagnosed in time, serious complications and even death appear [7]. Due to the variety of clinical manifestations and anatomical forms of the disease, a large number of patients have been subjected to wrong treatment even for several years, and their timely treatment is delayed. Obvious complications after surgery have been reported to be associated with different degrees of intestinal dysganglionosis and neuronal dysplasia [8, 10].

Hirschsprung-associated enterocolitis (HAEC) is the main cause of morbidity and mortality in children with HD. Meanwhile, its highly variable and non-specific clinical nature often leads to a late and/or incorrect diagnosis [7]. Accordingly, this study is intended to identify the clinical risk factors associated with pediatric HAEC.

MATERIALS AND METHODS

Study design and methods

All patients diagnosed with HD who were admitted to the hospital and met the inclusion criteria were recruited in this prospective observational study. Demographic and clinical data were obtained from their medical files and recorded. The criteria proposed by Pastor et al. [11] were used to diagnose HAEC. Inclusion criteria included children (under 8 years of age) diagnosed with biopsy-proven HD and those who also had informed parental consent. Patients who had a history of anorectal surgery and those who were lost to follow-up and/or gave no informed consent were excluded from the study.

The diagnosis was based on abdominal X-ray examination, rectal contrast injection (water contrast in childrens, bariatric contrast in older children), and rectal manometry. Also, biopsy specimens from rectal mucosa and muscles were collected and sent to the laboratory for histopathological and histochemical evaluations. During the diagnosis and treatment period, all the demographic and clinical data were prospectively collected and recorded for analysis.

Ethical approval

All procedures involving human participants were in accordance with the ethical standards of the national research committee and with the 2008 Helsinki Declaration and its later amendments. This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, with an Ethical Code: IR.AJUMS.HGOLESTAN.REC.1400.121.

Statistical analysis

SPSS 26 statistical software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Categorical variables were compared using the chi-square test and presented as frequency and percentages, while continuous variables were compared using paired samples Wilcoxon test and/or the paired t-test based on their normality nature.The P-value < 0.05 was regarded as statistically significant.

RESULTS

In this study, a total of 75 patients with HD were assessed, of which 18 cases (24%) had HAEC and the other 57 cases (76%) had Hirschsprung's disease. Demographics, clinical and paraclinical findings were compared between these two groups of patients. The results showed that there was no significant difference in terms of mean age between the two groups (P = 0.72). Also, the gender distribution was not significantly different between the two groups (P = 0.51). Two patients (3.5%) in the merely Hirschsprung group and one patient (5.5%) in the HAEC group had a family history of this disease, and this difference was not statistically significant (P = 0.25) (Table 1).

Moreover, no significant difference in the rates of diarrhea (P = 0.59) and colicky pain (P = 0.99) was observed between the two groups. However, the rates of abdominal distension (P = 0.02) and lethargy (P = 0.01) were significantly higher among children with HAEC (Table 1).

The radiology examination of the patients showed that 5 patients (8.8%) with HD and 9 patients (50%) with HAEC had dilated loops of bowel in their abdominal and pelvic x-rays, which was significantly different (P = 0.0001). The incidence rate of pneumoperitoneum was higher in children with HAEC than those with HD, but not significantly so (P = 0.58). Pneumatosis (the presence of gas within the bowel wall in radiography) was not observed in any of the children with HAEC, while it was found among merely 4 (7%) patients with HD. Anyway, this difference in the rate between the two groups was not statistically significant (P = 0.56). Also, the rectosigmoid cut-off sign was observed in 66.7% of patients with HAEC, which was significantly higher than its rate in those with HD (29.82%, P = 0.01) (Table 1).

Based on the paraclinical assessments, no significant difference was found between the two groups in terms of leukocytosis (P = 0.46) and the incidence rate of short and/or long-segment colon aganglionosis (P = 0.65). However, the incidence rate of sepsis

Table 1. Comparison of demographic, clinical, and paraclinical characteristics between patients with Hirschsprung's disease (HD) and those with Hirschsprung-associated enterocolitis (HAEC)

Variables	HD (n = 57)	HAEC (n = 18)	P Value
Age (month), mean±SD	28.5 ± 9.4	30.2 ±11.6	0.72
Gender: Boy Girl	 43 (75.4%) 14 (24.6%)	 12 (66.7%) 6 (33.3%)	0.51
Family history of HD	2 (3.5%)	1 (5.5%)	0.25
Diarrhea	30 (52.6%)	10 (55.5%)	0.59
Colicky Pain	26 (45.6%)	8 (44.5%)	0.99
Abdominal bloating and distension	17 (29.8%)	11 (61.11%)	0.02 OR(95% CI):2.049 (1.191_3.525) Chi^2 = 5.724
Lethargy	3 (5.3%)	5 (27.8%)	0.01 OR(95% CI): 5.278 (1.396_19.949) Chi^2 = 7.277
Dilated loops of bowel	5 (8.8%)	9 (50%)	0.0001 OR(95% CI): 5.7 (2.191_14.83) Chi^2 = 15.316
Pneumoperitoneum	3 (5.3%)	2 (11.1%)	0.58
Leukocytosis	37 (65%)	12 (66.7%)	0.99
Sepsis	2 (3.5%)	4 (22.2%)	0.027 OR(95% CI): 5.7 (2.191_14.83) Chi^2 = 6.509
Colon aganglionosis:			
Long segment	21 (36.8%)	6 (33.3%)	0.65
Short segment	36 (63.2%)	12 (66.7%)	
Pneumatosis	4 (7%)	0	0.56
Rectosigmoid cut-off sign	17 (29.8%)	12 (66.7%)	0.01 OR(95% CI):2.23 (1.33_3.74)

was significantly higher in children with HAEC than in those who had HD (P = 0.001). (Table 1).

DISCUSSION

Successful treatment of childrens and children with HD depends on prompt diagnosis and early treatment. If the disease is not diagnosed on time, serious complications of the disease such as enterocolitis, intestinal pneumatosis, rupture of the appendix, exudative enteropathy, growth disorder, toxic megacolon and even death will appear [12].

Hirschsprung-associated enterocolitis has been described as a separate syndrome that is clinically characterized by abdominal distension, diarrhea, colic pain, and sepsis [13]. This complication can occur at any time during the disease progression, and its incidence has been reported from 17% to 50% [14]. In the present study population, HAEC has been diagnosed in 24% of patients, which was notable.

Based on the findings of the present study, the mean age of patients with HAEC was not significantly different from non-enterocolitis patients. Also, the relative frequency of gender and family history of the disease were not significantly different between the two groups. Yulianda et al (2019) have previously pointed out that there was no association between the age of HD onset, gender, and maternal age in patients from Indonesia [15].

In the present study, no association was found between aganglionosis length and HAEC, which confirms the results of Yulianda et al. and Demehri et al. studies [15, 16]. In contrast to our findings, older research reported that the incidence of HAEC is higher in patients with long-segment aganglionosis than in short-segment patients [17, 19]. This discrepancy may be due to genetic, racial and ethnic differences of patients from different regions of the world.

In the present study population, the incidence of abdominal distension (61.11%) and lethargy (27.8%) were significantly higher among children with HAEC than those with HD (29.8% and 5.3%, respectively), which confirms the previous reports [15, 17]. However, the rates of these symptoms in our study population were significantly lower than in Yulianda et al.'s study population. Moreover, the incidence of dilated loops of bowel, rectosigmoid cut-off sign and sepsis were significantly higher in HAEC patients. Although pneumoperitoneum was more prevalent in HAEC patients, the difference in its rate between the two groups was not statistically significant, which may be due to the relatively small sample size. Overall, the most common clinical symptoms of HAEC in our study population were, respectively, abdominal distension (61.11%), dilated loops of bowel (50%), lethargy (27.8%), sepsis (22.2%), and pneumoperitoneum (11.1%). Also, the rectosigmoid cut-off sign was the most common radiological finding in HAEC (66.7%). Sepsis was not clearly assessed in any of the previous studies. Our confirmatory reports emphasize that these clinical symptoms can be considered diagnostic criteria for HAEC. By contrast, neither diarrhea nor colic pain were among the differential or specific symptoms of HAEC, which confirms the previous reports that pointed out none of these two symptoms as the main complaints of patients [20-22].

The present study did not find any significant association between leukocytosis and HAEC, which is in agreement with some of the previous reports [15, 22, 23]. Leukocytosis can be indicative of a range of disorders, including inflammation, infections and immune system disorders [24, 25]. In contrast to our finding, Gunadi et al. reported leukocytosis as one of the most specific signs of HAEC [26]. A definitive judgment in this regard requires multi-center research in a larger sample size. Overall, the present study is one of the few clinical studies in Iran that adds debatable and comparative findings to the scientific literature about critical HD and HAEC diseases in children in southwestern Iran.

CONCLUSION

Clinical symptoms of abdominal distension, dilated loops of bowel, lethargy, sepsis, and pneumoperitoneum as well as the rectosigmoid cut-off sign on the CT-scanogram may specifically indicate and differentiate HAEC in children with Hirschsprung's disease, which should be promptly diagnosed and treated. Nevertheless, further multicenter and prospective research in the larger population is recommended to accurately investigate the clinical and paraclinical factors associated with HAEC and its related adverse outcomes.

Conflict of Interest Statement: *The authors declare no conflicts of interest related to this work.*

Funding: *The authors did not receive any financial support from any organization for this research work.*

Ethics statement: *All procedures involving human participants were in accordance with the ethical standards of the national research committee and with the 2008 Helsinki Declaration and its later mendments.*

Ethical approval: *This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical*

Sciences, Ahvaz, Iran, with an Ethical code: IR.AJUMS. HGOLESTAN. REC.1400.121.

Informed Consent from Participants: *Informed consent was obtained from all participants (parents/guardians) included in the study.*

REFERENCES

1. Ali A, Haider F, Alhindi S. The Prevalence and Clinical Profile of Hirschsprung's Disease at a Tertiary Hospital in Bahrain. Cureus. 2021; 13(1):e12480.
2. Karami H, Mousavi A, Khademloo M, Soleimani F. Etiology of chronic constipation and related causes in children referred to Boo-Ali Sina Hospital in Sari between 2006 and 2007. Journal of Birjand University of Medical Sciences. 2009; 16(4):51-6.
3. Diposarosa R, Bustam NA, Sahiratmadja E, et al. Literature review: enteric nervous system development, genetic and epigenetic regulation in the etiology of Hirschsprung's disease. Heliyon. 2021; 7(6):e07308.
4. Lotfollahzadeh S, Taherian M, Anand S. Hirschsprung Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK562142/
5. Szylberg Ł, Marszałek A. Diagnosis of Hirschsprung's disease with particular emphasis on histopathology. A systematic review of current literature. Przeglad gastroenterologiczny. 2014; 9(5):264.
6. Ambartsumyan L, Smith C, Kapur RP. Diagnosis of Hirschsprung disease. Pediatric Developmental Pathology. 2020;23(1):8–22.
7. Langer JC, Levitt MA. Hirschsprung disease. Current Treatment Options in Pediatrics. 2020;6:128-39.
8. Gad El-Hak NA, El-Hemaly MM, Negm EH, et al. Functional outcome after Swenson's operation for Hirshsprung's disease. Saudi J Gastroenterol. 2010;16(1):30-4.
9. Peters NJ, Menon P, Rao KLN, Samujh R. Modified Duhamel's Two-Staged Procedure for Hirschsprung's Disease: Further Modifications for Improved Outcomes. J Indian Assoc Pediatr Surg. 2020;25(5):269-275.
10. Swaminathan M, Oron AP, Chatterjee S, et al. Intestinal Neuronal Dysplasia-Like Submucosal Ganglion Cell Hyperplasia at the Proximal Margins of Hirschsprung Disease Resections. Pediatr Dev Pathol. 2015;18(6):466-76.
11. Pastor AC, Osman F, Teitelbaum DH, et al. Development of a standardized definition for Hirschsprung's-associated enterocolitis: a Delphi analysis. Journal of pediatric surgery. 2009;44(1):251-6.
12. Gosain A, Frykman PK, Cowles RA, et al. American Pediatric Surgical Association Hirschsprung Disease Interest Group. Guidelines for the diagnosis and management of Hirschsprung-associated enterocolitis. Pediatr Surg Int. 2017; 33(5):517-521.
13. Lewit RA, Kuruvilla KP, Fu M, Gosain A. Current understanding of Hirschsprung-associated enterocolitis: Pathogenesis, diagnosis and treatment. Semin Pediatr Surg. 2022; 31(2):151162.
14. Hagens J, Reinshagen K, Tomuschat C. Prevalence of Hirschsprung-associated enterocolitis in patients with Hirschsprung disease. Pediatr Surg Int. 2022; 38(1):3-24.
15. Yulianda D, Sati AI, Makhmudi A, Gunadi. Risk factors of preoperative Hirschsprung-associated enterocolitis. BMC Proc. 2019; 13(Suppl 11):18.
16. Le-Nguyen A, Righini-Grunder F, Piche N, et al. Factors influencing the incidence of Hirschsprung associated enterocolitis (HAEC). J Pediatr Surg. 2019; 54(5):959-963.
17. Elhalaby EA, Teitelbaum DH, Coran AG, Heidelberger KP. Enterocolitis associated with Hirschsprung's disease: a clinical histopathological correlative study. J Pediatr Surg. 1995; 30:1023–1027.
18. Lacher M, Fitze G, Helmbrecht J, et al. Hirschsprung-associated enterocolitis develops independently of NOD2 variants. J Pediatr Surg. 2010; 45:1826–1831.
19. Lee CC, Lien R, Chiang MC, et al. Clinical impacts of delayed diagnosis of Hirschsprung's disease in newborn childrens. Pediatr Neonatol. 2012; 53(2):133-7.
20. Prato AP, Rossi V, Avanzini S, et al. Hirschsprung's disease: what about mortality? Pediatric surgery international. 2011; 27(5):473-8.
21. Gad El-Hak NA, El-Hemaly MM, Negm EH, et al. Functional outcome after Swenson's operation for Hirshsprung's disease. Saudi J Gastroenterol. 2010;16(1):30-4.
22. Sellers M, Udaondo C, Moreno B, et al. Enterocolitis asociada a enfermedad de Hirschsprung: estudio observacional sobre clínica y manejo en un servicio de urgencias hospitalarias / Hirschsprung-associated enterocolitis: Observational study in a paediatric emergency care unit. An. Pediatr. 2018; 88(6):329-334.
23. 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.
24. Velikov P, Kapincheva N, Trifonova I, et al. SARS-CoV-2 infection in children and young people in Bulgaria – a prospective, single-center, cohort study. Acta Medica Bulgarica 2023; 50(2):10-19. https://doi.org/10.2478/AMB-2023-0014
25. Ivanov N, Mihailova S, Bilyukov R, et al. Changes in the cytokine profile in patients during COVID-19 infection. Acta Medica Bulgarica 2023;50(4):5-12. https://doi.org/10.2478/AMB-2023-0036
26. Gunadi, Ningtyas HH, Simanjaya S, e. Comparison of preoperative Hirschsprung-associated enterocolitis using classical criteria and Delphi method: A diagnostic study. AMS. 2020;51:37-40.