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ORIGINAL ARTICLE

The relationship of eosinophilia with outcomes of Hirschsprung disease in children

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Abstract

Purpose It has been postulated that children with Hirschsprung disease (HD) and mucosal eosinophilia have been thought to have poorer outcome, but supporting evidence is lacking. The objective of our study was to review the outcomes of children with HD and mucosal eosinophilia.

Methods A single center, retrospective review was conducted on all patients diagnosed with HD between 1999 and 2016. Pathology specimens were evaluated for mucosal eosinophilia. Demographics, complications, and outcomes were analyzed.

Results A total of 100 patients were diagnosed with HD and 27 had mucosal eosinophilia. Median age at the time of surgery was 12 days (8, 30) and 82 were males. Comparing patients with HD with and without mucosal eosinophilia, there was no statistically significant difference in time to bowel function (2 days vs. 2 days; $p=0.85$), time to start feeds (3 days vs. 3 days; $p=0.78$) and time to goal feeds (5 days vs. 5 days; $p=0.47$). There was no statistically significant difference in feeding issues (13% vs. 9%; $p=1.0$) and stooling issues (60% vs. 50%; $p=0.38$). There was no statistically significant difference in postoperative complications and readmissions rates (63% vs. 56%; $p=0.53$).

Conclusion Hirschsprung-associated mucosal eosinophilia may not increase postoperative complications, and may not change feeding and bowel management. Further prospective studies are in process to evaluate long term follow-up outcomes for this patient population.

Keywords Hirschsprung disease · Children · Eosinophilia

Introduction

Hirschsprung disease is one of the most common causes of neonatal bowel obstruction with an incidence of 1 to 5000–10,000 in the USA and Europe [1, 2]. After surgery, children may experience issues that include enterocolitis, obstructive symptoms, soiling, and failure to thrive [3–5]. Patients may continue to suffer from abnormal bowel function well into adulthood [6, 7].

Mucosal eosinophilia-associated gastrointestinal disorders are rare and include issues that occur from the esophagus to the rectum [8–11]. Newborn children with eosinophilia on rectal biopsies with no evidence of Hirschsprung disease have been found to have a higher percentage of gastrointestinal symptoms compared to those without eosinophilia [12]. Yet, there has only been case reports regarding patients with mucosal eosinophilia associated with Hirschsprung disease and there is a paucity of literature regarding their outcomes [13]. There had been a perception at our institution that children with mucosal eosinophilia associated with Hirschsprung disease had more short- and long-term issues with bowel function and feeding intolerance compared to those without. Therefore, evaluation of patient outcomes was necessary.

The objective of our study was to review the outcomes of children with Hirschsprung disease and mucosal eosinophilia at our institution. Given children with mucosal eosinophilia tend to suffer from a higher rate of gastrointestinal problems, we hypothesized that children with Hirschsprung

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disease and mucosal eosinophilia would also suffer from an increased incidence of stooling and feeding difficulties.

Materials and methods

Following approval by the Institutional Review Board (IRB) of Children's Mercy Hospital (IRB#16070512), medical records of all children less than 18 years old with Hirschsprung disease were retrospectively reviewed from January 1999 to July 2016. Patients were identified based on International Classification of Disease Ninth Revision (ICD-9) diagnosis coding for Hirschsprung disease (ICD-9: 751.3). We included those patients that underwent their suction or full thickness rectal biopsy at Children's Mercy Hospital and were pathologically proven to have Hirschsprung disease. The biopsies were stained with haematoxylin and eosin and calretinin immunochemistry. The diagnosis of tissue mucosal eosinophilia was confirmed by identifying mucosal eosinophils within the biopsied rectal tissue and final resected specimens. We reviewed the final pathology reports of the rectal biopsies and the final resected specimens. Those that underwent their operation at Children's Mercy Hospital were also included. We excluded patients who underwent biopsies and operations at outside institutions, those with a diagnosis other than Hirschsprung disease, and rectal biopsies without sufficient specimen for a diagnosis.

Patient demographics including age and gender were collected. Rectal biopsy results including the presence of ganglion cells and/or mucosal eosinophils were reported. The presence of mucosal eosinophils on final pathology was reviewed. Postoperative outcomes include time to bowel function, time to feeding, and complications. Feeding and stooling issues were identified at any documented follow-up. Feeding issues were classified as: milk intolerance, failure to thrive, reflux, food causing constipation. Stooling issues were classified as: incontinence, constipation, high ostomy output, fecal impaction, obstipation. Follow-up outcomes include readmissions, need for gastroenterology follow-up, need for further workup with endoscopy and anal manometry, and need for bowel management program.

Descriptive statistics including counts and percentages were analyzed. Pearson's Chi square and Fisher's exact tests were used for categorical variables, and the frequencies were reported as a percentage of the group of origin. Mann–Whitney U test was utilized for continuous variables and the frequency of continuous variables was reported as median and interquartile range (IQR). Statistical significance was set at $p < 0.05$, and all reported p values were two tailed. Statistical analysis was performed using IBM SPSS Statistics (Version 23, IBM Corp., Armonk, NY).

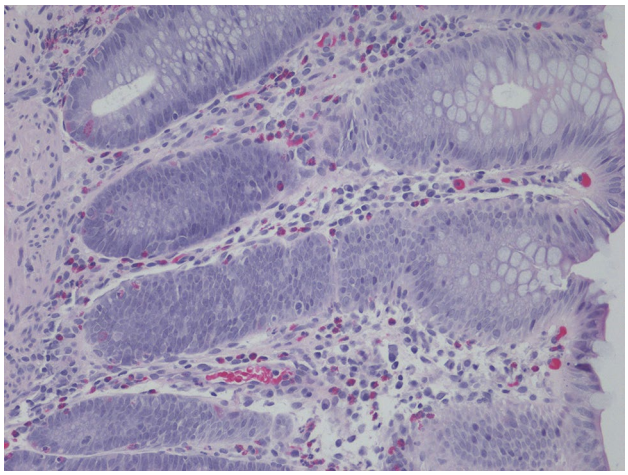

Fig. 1 Rectal mucosa showing increased eosinophils in the lamina propria (H&E stain, ×200 magnification)

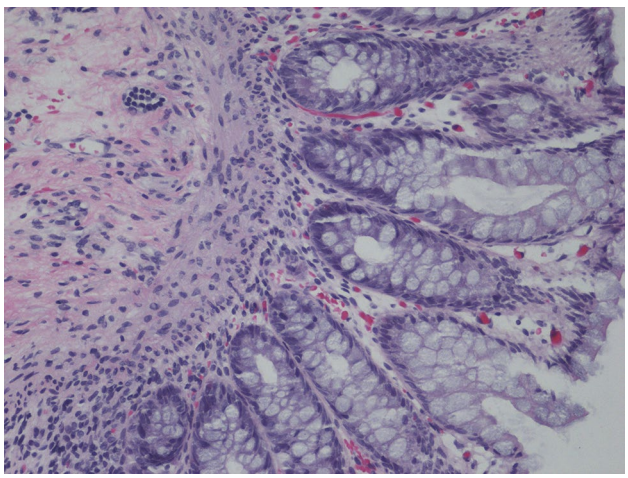

Fig. 2 Rectal mucosa from a patient with no increase in eosinophils (H&E stain, ×200 magnification)

Results

From 1999 to 2016, 100 patients were diagnosed with Hirschsprung disease and 27 were found to have mucosal eosinophils on rectal biopsies and/or resected specimens. Fifteen had mucosal eosinophilia found on rectal biopsy (suction or full thickness) and 12 on resected specimens only (Fig. 1). The remaining 63 did not have eosinophilia (Fig. 2). There were three that were found to have mucosal eosinophilia both on rectal biopsy and resected specimens. Pathology reports were reviewed for the presence of ganglion cells. Slide review is planned for a subsequent study. Pathologists at our institution use a standard cutoff for colonic mucosal eosinophils, which varies with the

segment of colon. For the rectum mucosa, the normal cut-off value is 19 per high power field (approximately, 95 eosinophils per square millimeter). There were 82 males and median age at the time of surgery was 12 days (8, 30). Postoperatively there was no statistically significant difference in time to bowel function (2 days vs. 2 days; $p=0.85$), time to start feeds (3 days vs. 3 days; $p=0.78$) and time to goal feeds (5 days vs. 5 days; $p=0.47$) when comparing those with and without mucosal eosinophilia. There was no difference in complications between both groups and there were three deaths (Table 1).

The median time to first follow-up from the time of surgery was 24 days (19, 39.5) with ten (10%) lost to follow-up. There was no statistically significant difference in the time to follow-up (24 days vs. 29 days; $p=0.70$) between those with or without mucosal eosinophilia. A total of 57 patients were readmitted and the most common reason was for enterocolitis (32%). There was no statistically significant difference in readmission rates (63% vs. 56%; $p=0.53$) and complications when comparing those with or without mucosal eosinophilia. There was no statistically significant difference with those undergoing repeat rectal biopsy (16% vs. 25%; $p=0.37$) and anal manometry (14% vs. 27%; $p=0.37$). Only ten patients underwent anal botulinum toxin injections and all of those patients did not have mucosal eosinophilia. There was no statistically significant difference in gastroenterology follow-up (32% vs. 44%; $p=0.27$) between both groups (Table 2).

There were a total of ten (10%) patients with feeding issues at any follow-up (milk intolerance = 3; failure to thrive = 5; reflux = 1; food causing constipation = 1). There were no statistically significant differences between those without or with mucosal eosinophilia (13% vs. 9%; p = 1.0).

Table 1 Demographics and immediate postoperative characteristics

	Without eosinophilia ($n=73$)	With eosinophilia ($n=27$)	p value
Male	59 (81%)	23 (85%)	0.77
Age (days)*	12 (8, 29)	12 (9, 27)	0.49
Time to bowel function (days)*	2 (2, 3)	2 (2, 3)	0.85
Time to start feeds (days)*	3 (2, 4)	3 (2, 4)	0.78
Time to goal feeds (days)*	5 (4, 7)	5 (4, 8)	0.47
Complications			
Enterocolitis	4 (6%)	1 (4%)	1.00
Sepsis	3 (4%)	0	0.56
Wound infection	4 (6%)	0	0.57
Other	4 (6%)	3 (12%)	0.38
Mortality	2 (3%)	1 (4%)	0.80
Reoperation	3 (4%)	4 (15%)	0.08

*Reported as median (IQR)

Table 2 Follow Up outcomes

	Without eosinophilia ($n=73$)	With eosinophilia ($n=27$)	p value
Time to first follow-up (days)	24 (19, 38)	29 (18, 55)	0.70
Readmitted	43 (63%)	14 (56%)	0.53
Constipation	16 (24%)	5 (20%)	0.67
Bowel obstruction	4 (6%)	0	0.57
Enterocolitis	24 (36%)	8 (35%)	0.89
Repeat rectal biopsy	11 (16%)	6 (25%)	0.37
Anal manometry	9 (14%)	6 (27%)	0.19
GI follow-up	21 (32%)	11 (44%)	0.27

GI Gastroenterology

*Reported as median (IQR)

There was no statistically significance difference in the time to feeding issues between both groups (683 days vs. 424 days; $p=0.77$). There were no formula changes for those with mucosal eosinophilia compared to four changes with those without mucosal eosinophilia; however, this was not a statistically significant difference ($p=0.56$). There was no statistically significant difference for achieving full feeds (96% vs. 91%; $p=0.58$) and tolerating solid foods (90% vs 76%; $p=0.38$) between both groups (Table 3).

There were 50 patients with stooling issues (incontinence = 12; constipation = 35; high ostomy output = 1; fecal impaction = 1; obstipation = 1). There was no statistically significant difference between both groups (60% vs. 50%; $p=0.38$). There was no statistically significance difference in the time to stooling issues at any follow-up between both groups (318 days vs. 274 days; $p=0.77$). 56 patients were involved in a bowel management program with no statistically significant difference between both groups (63% vs. 56%; $p=0.56$) (Table 3).

Discussion

This is the first study to date to review the outcomes of children with Hirschsprung disease and tissue mucosal eosinophilia. We found no statistically significant difference in postoperative outcomes and complications for children with or without mucosal eosinopilia. There was also no statistically significant difference in feeding and stooling issues during their outpatient follow-up.

Currently, there have been only case reports of mucosal eosinophilia associated with Hirschsprung disease [13, 14]. Eosinophilia esophagitis, gastritis, gastroenteritis and colitis are rare diseases, but have been extensively studied [8–11, 15]. These children can present with gastrointestinal symptoms such as diarrhea, abdominal pain

Table 3 Feeding and stooling outcomes

	Without eosinophilia ($n=73$)	With eosinophilia ($n=27$)	p value
Feeding issues at any follow-up	8 (13%)	2 (9%)	1.0
Time to feeding issues (days)*	683 (89,1351)	424 (407,440)	0.77
Formula changes	4 (7%)	0	0.56
Achievement of full feeds	52 (96%)	21 (91%)	0.58
Tolerating solid foods	56 (90%)	19 (76%)	0.10
Stooling issues at any follow-up	38 (60%)	12 (50%)	0.38
Time to stooling issues (days)*	318 (120,884)	274 (253,566)	0.73
Bowel management program	42 (63%)	14 (56%)	0.56

*Reported as median (IQR)

and obstruction [9, 16]. Pacilli et al. reviewed the rectal biopsies of children, but excluded those with Hirschsprung disease. They found those with mucosal eosinophilia had a high percentage that suffered from constipation and failure to thrive [12]. Children with Hirschsprung disease can suffer from constipation, soiling difficulties and obstructive symptoms postoperatively, which can lead to significant morbidity [1, 3, 5, 17]. In our practice, there were concerns that children with mucosal eosinophilia-associated Hirschsprung disease suffered from worse outcomes, especially with regard to feeding and stooling issues. However, our retrospective review showed that these children have similar outcomes compared to those without mucosal eosinophilia.

Limitations of our study include the inherent nature of a retrospective review and we were limited to information in the medical record. While we did lose 10% of patients to follow-up, this is still the largest series of patients reviewed with mucosal eosinophilia and Hirschsprung disease. While a high percentage of patients had stooling issues and were on a bowel management program, less than 45% were seen by gastroenterology and less than 30% underwent manometry. This shows a need for standardized multidisciplinary postoperative care and future prospective studies evaluating standardized care in these patients. Moreover, these patients and all new patients diagnosed with Hirschsprung disease at our hospital will be followed prospectively for the next 5 years to allow continued long-term outcome evaluation.

Conclusion

Our series indicates Hirschsprung-associated mucosal eosinophilia may not increase postoperative complications and may not change feeding and the need for bowel management regimens. Further prospective studies are in process to evaluate long-term follow-up outcomes for this patient population.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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