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Hirschsprung-associated inflammatory bowel disease: A multicenter study from the APSA Hirschsprung disease interest group

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ABSTRACT

Background/Purpose: A small number of Hirschsprung disease (HD) patients develop inflammatory bowel disease (IBD)-like symptoms after pullthrough surgery. The etiology and pathophysiology of Hirschsprung-associated IBD (HD-IBD) remains unknown. This study aims to further characterize HD-IBD, to identify potential risk factors and to evaluate response to treatment in a large group of patients.
Methods: Retrospective study of patients diagnosed with IBD after pullthrough surgery between 2000 and 2021 at 17 institutions. Data regarding clinical presentation and course of HD and IBD were reviewed. Effectiveness of medical therapy for IBD was recorded using a Likert scale.
Results: There were 55 patients (78% male). 50% (n = 28) had long segment disease. Hirschsprung-associated enterocolitis (HAEC) was reported in 68% (n = 36). Ten patients (18%) had Trisomy 21. IBD was diagnosed after age 5 in 63% (n = 34). IBD presentation consisted of colonic or small bowel inflammation resembling IBD in 69% (n = 38), unexplained or persistent fistula in 18% (n = 10) and unexplained HAEC >5 years old or unresponsive to standard treatment in 13% (n = 7). Biological agents were the most effective (80%) medications. A third of patients required a surgical procedure for IBD.
Conclusion: More than half of the patients were diagnosed with HD-IBD after 5 years old. Long segment disease, HAEC after pull through operation and trisomy 21 may represent risk factors for this condition. Investigation for possible IBD should be considered in children with unexplained fistulae, HAEC beyond

Abbreviations: APSA-HDIG, the American Pediatric Surgical Association Hirschsprung Disease Interest Group; HD, Hirschsprung disease; HAEC, Hirschsprung associated enterocolitis; IBD, inflammatory bowel disease; HD-IBD, Hirschsprung-associated inflammatory bowel disease; FH, family history; CD, Crohn disease; UC, ulcerative colitis.

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the age of 5 or unresponsive to standard therapy, and symptoms suggestive of IBD. Biological agents were the most effective medical treatment.
Level of Evidence: Level 4

1. Introduction

Hirschsprung disease (HD) or congenital aganglionosis is a developmental disorder of the enteric nervous system characterized by the absence of ganglion cells in the myenteric and submucosal plexuses of the intestine [1]. The incidence of HD is 1 in 5000 live births [2] and most of the patients are diagnosed and undergo definitive operation within the first year of life [3]. IBD in children who have undergone surgery for HD is a rare condition with a reported incidence of 2% [4]. This condition was first reported in 1989 [5] and we also reported a detailed case series of 8 HD patients who developed IBD after pull through operation in 2012 [6]. Since then, there have been several small studies reporting further patients with this condition [4,7,8]. There was a higher incidence of Crohn's disease than ulcerative colitis after pullthrough surgery in these studies,[6-8]. The etiology and pathogenesis of this condition remains unknown. Based on our experience, we hypothesized that there are clinical risk factors that predispose patients with HD to develop IBD. The primary objectives of this study were to further characterize HD-associated IBD, to identify potential risk factors, and to gain some insights into the effectiveness of various forms of therapy for HD-IBD.

2. Methods

2.1. Study design and data source

This was a retrospective multi-center study sponsored by the American Pediatric Surgical Association Hirschsprung Disease Interest group (HDIG). The HDIG is a large group of pediatric surgeons in the USA, Canada, Australia, Mexico and Argentina who have a focused interest in the management of children with HD. The Hospital for Sick Children was the coordinating center (Research Ethics Board approval number 1000070280) and each of the other institutions obtained their own Institutional Review Board approval.

2.2. Inclusion criteria

Patients who were diagnosed with HD between 0 and 18 years of age who subsequently developed at least one of three clinical scenarios of IBD-like symptoms between January 1, 2000 and February 10, 2021 were included in the study. The three categories of IBD-like symptoms included: 1. Unexplained or persistent colocutaneous, colo-enteric, colo-vesical or colo-vaginal fistulae; 2. Inflammation in the colon or small bowel which resembled Crohn disease or ulcerative colitis endoscopically and/or histologically; or 3. Ongoing HAEC in children over 5 years of age without an underlying cause for obstruction or children at any age who had not responded to standard therapy for HAEC.

2.3. Data collection

Study data were collected and managed using REDCap electronic data capture tools [9,10] hosted at the Hospital for Sick Children. Demographic data, level of transition zone, type of pull-through, incidence of HAEC, family history of HD or IBD, associated genetic abnormalities, clinical presentation and course of HD and IBD were reviewed. Effectiveness of medical therapy for IBD was recorded and assessed using a Likert scale based on the information provided by surgeons at each institution based on information that was available from the hospital charts.

Data were validated by clarifying that each hospital obtained all the information from the patient's chart and recorded all the information in a standardized way in RedCap. The data were then verified with them after entry.

2.4. Statistical analysis

This was a descriptive study without a control group. Categorical data were presented as frequencies and proportions. Continuous data were presented as median, range and IQR. The Likert scale data were converted to three categories: ineffective (Likert 1–3), partially effective (Likert 4–6) and effective (Likert 7–9). Descriptive statistics were performed using RedCap version 12.3.3 (2022, Vanderbilt University). Missing data were excluded from the analysis.

3. Results

3.1. Study population

There were 55 patients contributed by 17 institutions. Patient demographics and clinical characteristics of HD are summarized in Table 1. The majority of the patients (98%) were born at full term. There were 12 female patients (22%) and 43 male patients (78%) with more than half of the patients (n = 31, 57%) being diagnosed with HD before the age of one month. Four patients (7%) had aganglionosis proximal to the splenic flexure, and 24 (43%) had total colonic aganglionosis (TCA). Preliminary stoma prior to pull-through operation was performed in 37 patients (67%).

Of the 52/55 patients in which the type of pull-through was known, Duhamel (17, 33%) and Soave (18, 33%) were the most common pull-through operations followed by Swenson in 10 patients (19%), laparoscopic assisted pull-through of unknown type in 4, total colectomy with J pouch in 1, total colectomy with end ileostomy in 1, and anorectal myomectomy in 1. Twenty-nine patients (57%) underwent a pull-through between 1 month and 1 year of life. Thirty-six patients (68%) experienced HAEC after the pull-through operation. Genetic mutation analysis for HD was done in 18 patients; 4 had a RET gene mutation and one had a ZEB2 mutation. Of the 55 patients, 8 (15%) had cardiac disease and 10 (18%) had trisomy 21. Syndromes were found in 3 patients, including Bardet-Biedl syndrome, Waardenburg syndrome and Mowat-Wilson syndrome. Forty-four patients (80%) underwent additional surgical procedures after pull-through surgery, including colonic biopsy in 16 patients (37%), botulinum toxin injection in 9 patients (21%), stoma revision in 11 patients (26%), colon resection in 9 patients (21%) and adhesiolysis for intestinal obstruction in 6 patients (14%).

Table 1
Demographic data and clinical characteristic of HD in 55 patients.

Characteristic	No. (%)[a]
Gender	
Male	43 (78)
Female	12 (22)
Gestational age	
Preterm (≤35 weeks)	1 (2)
Term (≥36 weeks)	48 (98)
Unknown	6
Age at diagnosis of HD	
<1 month	31 (57)
1 month - 1 year	15 (28)
1–3 years	2 (4)
>3 years	6 (11)
Unknown	1
Level of Transition Zone	
Short segment	
Recto sigmoid	24 (44)
Left colon	3 (5)
Long segment	
TC/Right colon	4 (7)
TCA	21 (38)
Mid-small bowel	3 (5)
Type of Pull through	
Swenson	10 (19)
Soave	18 (35)
Duhamel	17 (33)
Other	7 (13)
Unknown	3
Age at Pull through	
< 1 month	6 (11)
1 month - 1 year	29 (55)
1–3 years	9 (17)
>3 years	9 (17)
Unknown	2
HD genetic mutation	
Yes	6 (33)
No	12 (67)
Not done	37
Episode of HAEC	
Yes	36 (68)
No	17 (32)
Unknown	2
Family history of HD	
Yes	12 (26)
No	35 (74)
Unknown	8
Cardiac condition	
Yes	8 (15)
No	46 (85)
Unknown	1
Trisomy 21	
Yes	10 (18)
No	45 (82)

Abbreviations: HD, Hirschsprung disease; TC, Transverse colon; TCA, Total colonic aglanglionosis; HAEC, Hirschsprung associated enterocolitis.
[a] Percentage excludes patients in which the value is unknown or not done.

3.2. IBD characteristics and treatment

The features of IBD in the study population are summarized in Table 2. Thirty-three patients (60%) presented with colonic or small bowel inflammation resembling CD, 10 (18%) developed unexplained or persistent fistula, 5 (9%) had endoscopic or histological evidence of UC and 7 patients (13%) had ongoing HAEC beyond the age of 5 without underlying obstruction, or at any age unresponsive to HAEC therapy. Clinical diagnosis of IBD by the treating team was Crohn disease in 39 patients (71%), UC in 5 (9%) and IBD-unclassified (IBD-U) in 11. The majority of patients (63%) developed IBD after 5 years of age. Family history of IBD was present in 20%. Serology for IBD markers was tested in 20 patients and found to be positive in 8 patients (Anti-*Saccharomyces cerevisiae* antibody (ASCA) in 1 and Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) in 3 and the specific marker was not identified in the chart in 4 patients) and all 8 patients were diagnosed with CD. The most common IBD presenting symptoms were demonstrated in Table 2. Six patients (11%) experienced extra intestinal manifestations of IBD, including leg pain, eosinophilic esophagitis, cheilitis, arthralgia and oral ulcers.

(Table 3) Pharmacological treatment for IBD was utilized in all 55 patients, including corticosteroids (n = 31, 57%), aminosalicylates (n = 25, 46%), immunomodulators (n = 14, 26%), biological agents (n = 26, 47%) and antibiotics (n = 38, 70%). Enteral metronidazole was the most common antibiotic regimen used. The most common medications given in CD patients were biologicals (67%), aminosalicylates (64%), corticosteroids (59%), and antibiotics (57%). Corticosteroids and aminosalicylates were the most common medications used for those with a diagnosis of UC. Biological agents were the most effective (80%), followed by corticosteroids (58%) and antibiotics (52%) (Fig. 1).

Sixteen patients (30%) required a surgical procedure for IBD, including seton placement (n = 5), ileocolectomy (n = 2), as well as redo pull-through, redo pull-through with colovesical fistula takedown, total colectomy with proctectomy and J-pouch anastomosis, diverted rectal stump due to prostatic fistula, gastrointestinal fistula closure, small bowel fistula takedown, rectal dilation, dilation of small bowel and colonic stent placement (all n = 1). Median patient age at last follow was 13 (range 5–46) years.

Table 2
HD-IBD characteristics.

Characteristics	N (%)[a]
Age at onset of IBD symptom	
1 month - 1 year	4 (7.5)
1–3 years	5 (9)
3–5 years	11 (20.5)
6–12 years	19 (35)
>13 years	15 (28)
Unknown	1
IBD type	
CD	39 (71)
UC	5 (9)
IBD-U	11 (20)
Serology	
Positive	8 (40)
Negative	12 (60)
Unknown/Not done	35
Family history of IBD	
Positive	9 (20)
Negative	36 (80)
Unknown	10
IBD specific presentation	
Colo-cutaneous/enteric/vaginal fistula	10 (18)
Intestinal inflammation resembling CD	33 (60)
Endoscopic or histologic evidence of UC	5 (9)
Ongoing HAEC > 5yo or unresponsive to standard HAEC therapy	7 (13)
IBD symptoms	
Diarrhea	35 (64)
Hematochezia	23 (42)
Abdominal pain	27 (49)
Growth failure	14 (25)
Anemia	2 (4)
Extraintestinal manifestation	
Yes	6 (11)
No	49 (89)
Surgical procedure for IBD	
Yes	16 (30)
No	38 (70)
Unknown	1

Abbreviations: HD-IBD, Hirschsprung-associated inflammatory bowel disease; IBD, inflammatory bowel disease; HAEC, Hirschsprung associated enterocolitis; CD, Crohn disease; UC, Ulcerative colitis.
[a] Percentage excludes patients in which the value is unknown or not done.

Table 3
Pharmacological therapy.

Medication N (%)[a]	HD-IBD (N = 55)	CD (N = 39)	UC (N = 5)	IBD-other (N = 11)
Corticosteroids	31 (70%)[a]	23 (64%)	4 (80%)	4 (36%)
Aminosalycylates	25 (57%)	16 (41%)	5 (100%)	4 (36%)
Antibiotics	38 (86%)	29 (74%)	2 (40%)	7 (64%)
Immunomodulators	14 (32%)	12 (31%)	1 (20%)	1 (90%)
Biologicals	26 (59%)	22 (56%)	2 (40%)	2 (18%)

Abbreviations: HD-IBD, Hirschsprung-associated inflammatory bowel disease; CD, Crohn disease; UC, Ulcerative colitis; IBD, inflammatory bowel disease.
[a] Values indicate the number of patients (%).

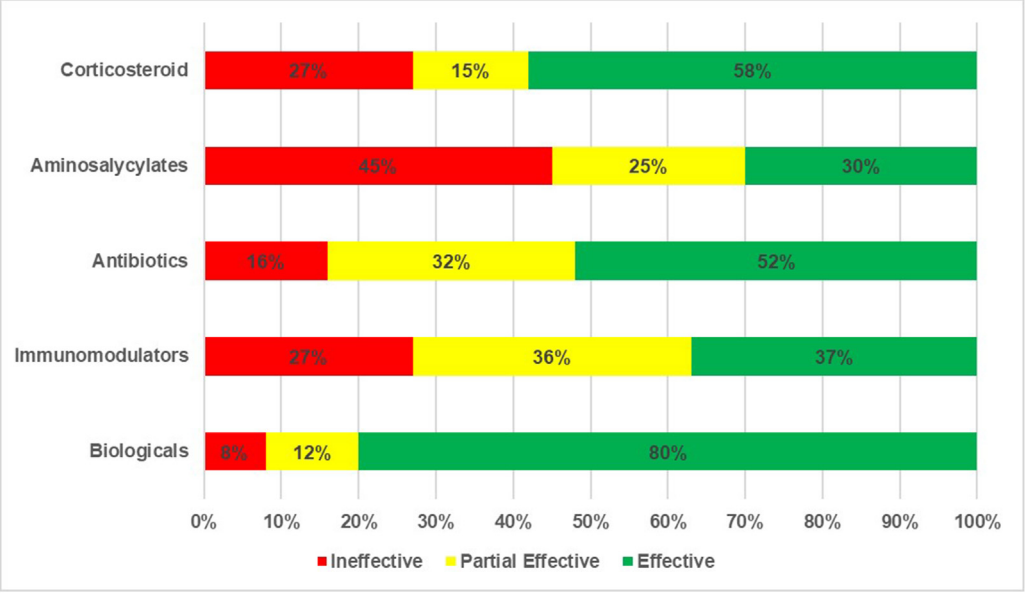

Fig. 1. The bar graph shows the effectiveness of each medication.

4. Discussion

This retrospective study represents the largest cohort of patients with Hirschsprung associated-IBD (HD-IBD) to date. The only previous case series consisted of 8 patients from two centers in 2012 [6]; the authors estimated that those 8 patients represented approximately 1% of their patients with HD over that time period. The first goal of our study was to determine if there are any risk factors for the development of IBD in patients who have had surgery for HD. Features that appeared to occur more often than expected in our series compared to the normal population of children with HD included long segment disease, trisomy 21, and a prior history of HAEC after pullthrough operation.

Based on the literature, approximately 5–10% of children with HD have total colonic aganglionosis (TCA) [11]. In contrast, 44% of the patients in our series of children with HD-IBD had TCA. Trisomy 21 has been reported in approximately 10% of the general population of HD patients [12,13]. In the present study we found trisomy 21 in 18% of the patients with HD-IBD. Finally, 68% of the patients in our study experienced episodes of HAEC after pull-through surgery. Patients with HD are at risk for Hirschsprung-associated enterocolitis (HAEC), which is an inflammatory disorder of unknown etiology which occurs prior to surgery in 15–50% of patients and can occur even after the aganglionic segment is removed in approximately 2–33% of patients [3,7,14,15]. This condition usually resolves after the first 5 years of life in the absence of an ongoing source of obstruction [1,6,12]. HAEC is thought to be more common in long segment disease and trisomy 21 [1,5,6,16], which were also overrepresented in our patients. It remains unclear whether HD-IBD is a consequence of ongoing HAEC or a separate condition with a different etiology.

The literature also supports long segment disease, trisomy 21, and postoperative HAEC as potential risk factors for HD-IBD. Our small series in 2012 found that 3 of the 8 HD-IBD patients had trisomy 21 and 6 had previous episodes of HAEC [6]. In the systematic review in 2018 Nakamura et al. conducted a meta-analysis of 14 studies of 66 patients and reported that 41% of the patients had TCA and 47% had past experience of HAEC [7].

In recent years, a number of studies have documented the presence of inflammatory bowel disease (IBD) in a small number of patients with HD following pull-through surgery [4,6–8]. IBD associated with HD was first reported in 1989 by Sherman et al. who in a retrospective study of 880 patients with HD reported 9 patients (1%) who developed IBD-like symptoms [17]. In 2018, the first population-based study from Sweden [8] reported a 2.7% incidence of IBD in patients with HD (OR of 4.99 (95% CI, 2.85–8.45)) vs those without HD. Median age at first diagnosis of IBD was 19 years (range 5–34). These data suggest that the estimated incidence of 1% in the previously mentioned studies might be low because of their shorter follow-up. Five of 18 patients (28%) in the Swedish study required surgical treatment for IBD, which is quite similar to our result.

A recent Canadian population-based controlled study in 2021 suggested that HD-IBD developed in approximately 2% of patients with HD. Mean age of first presentation of IBD was 7.5 years [4]. The youngest age at diagnosis of HD-IBD reported in the literature was in a 12-month-old patient who had long-segment HD (transition zone in the jejunum at 72.5 cm proximal to the ileocecal valve). This

patient had several episode of bright red blood per rectum and eventually was treated with corticosteroids and infliximab with full clinical remission [18]. This is consistent with very-early-onset IBD (VEOIBD) less than 6 years of age [19]. In our study, there were 20 patients (36%) diagnosed with HD-IBD before the age of 5.

The most common form of HD-IBD in our study was CD, which is consistent with the previous studies [4,6–8]. Sixty-nine% of patients in our study had an endoscopic finding resembling CD or UC, 18% presented with persistent fistulae and 13% of patients had ongoing HAEC beyond 5 years of age or unresponsive to standard HAEC treatment. These 3 presentations are different from typical HAEC, which characteristically responds to treatment with irrigation, antibiotics, and fluid resuscitation, and which usually resolves by age 5 [3].

CD, UC, and IBD-U are idiopathic, chronic inflammatory intestinal disorders. Approximately 25% of IBD patients are diagnosed before the age of 18 [20] with an incidence of 10 per 100,000 children in the United states and Canada [21–23]. According to previous publications and the current study, the onset of HD-IBD appears to be earlier than typical pediatric IBD. Almost 50% of patients in our study developed IBD before or at 5 years of age. The etiology of IBD is multifactorial, involving genetic predisposition, mucosal barrier dysfunction, disturbances in the gastrointestinal microbiota, dysregulated immune response, environmental, and lifestyle factors [22]. The most common presenting symptom in UC is bloody diarrhea whereas CD may present with vague abdominal pain, diarrhea, unexplained anemia, fever, weight loss, or growth retardation [22]. All of these symptoms were also found among the patients with HD-IBD in our study. The most common symptoms of HD-IBD in our study were diarrhea, hematochezia, abdominal pain and growth failure. ASCA is more common in CD (50–70%) than in UC (10–15%) and p-ANCA is detected in the serum of 60–70% of UC while in only 15–25% of patients with CD [22,24]. Unfortunately, we did not have serology data on enough patients to investigate its usefulness in the diagnosis of HD-IBD.

The goal of IBD therapy is to achieve remission of active disease, suppression of inflammation, optimization of growth through adequate nutrition, and improvement in quality of life while minimizing drug toxicity [23,25]. A variety of pharmacological agents have been used, including corticosteroids, aminosalicylates, immunomodulators, and biological agents, along with surgical resection in some cases [25,26]. All of these treatment modalities were used to a variable extent in our series of patients with HD-IBD. The second goal of our study was to determine the effectiveness of these treatment modalities in children with HD-IBD. Corticosteroids, antibiotics and biologicals were the most common medications used for HD-IBD in our study and these 3 medications were rated effective on the Likert scale in more than 50% of patients. The 5 patients with a picture of UC in our study were all treated with aminosalicylates with an effective response in 3 of the patients. Aminosalicylates were ineffective in almost half of our CD patients, which is consistent with the literature for the general CD population [23,25].

5. Limitations

This study has several limitations. Because it is a multicenter retrospective study, information may not have been consistently recorded, and there is therefore a risk of selection and reporting bias. There were no single diagnostic criteria for IBD and the differentiation of CD from UC may be subjective and variable from center to center, based on the combination of history, physical and laboratory examination, esophagogastroduodenoscopy (EGD) and ileocolonoscopic with histology, and imaging of the small bowel [20,24]. Moreover, there is no standard criteria for diagnosis of HAEC. For all these reasons, our study has the potential for information bias. Patients in our cohort study received a variety of therapeutic agents; given the small number of patients receiving each medication, as well as the heterogeneity of regimens, timing, and surveillance, we cannot draw any firm conclusions about medical treatment from this study. Similarly, the use of the Likert scale based on clinical response rating by the surgeon who collected the data is subjective and at risk for response bias. However, these are the first data to be reported about response of HD-IBD to treatment and need to be followed by a more rigorous and detailed analysis in a larger group of patients.

6. Conclusion

This is the largest cohort study on HD-IBD to date. HD-IBD can develop any time after pull through operation, however, more than half of the patients were diagnosed with IBD after 5 years old. This condition has a variable presentation, often many years after pull through surgery. Long segment disease, post-pull through enterocolitis, and trisomy 21 may represent risk factors for this condition. HD-IBD should be considered in patients with HD who have a picture of CD or UC, non-healing fistulas, HAEC after age 5 in the absence of an obstructive cause, or HAEC unresponsive to standard therapy prior to age 5. HD-IBD appears to be most responsive to pharmacological treatment using corticosteroids, antibiotics and biologicals, and surgery was required in a third of children.

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Conflict of interest

The authors declare that the research was conducted in the absence of conflict of interest.

References

[1] Langer JC, Levitt MA. Hirschsprung disease. Current treatment options in pediatrics 2020;6(3):128–39. https://doi.org/10.1007/s40746-020-00195-3.
[2] Nasr A, Sullivan KJ, Chan EW, Wong CA, Benchimol EI. Validation of algorithms to determine incidence of Hirschsprung disease in Ontario, Canada: a population-based study using health administrative data. Clin Epidemiol 2017;9:579–90. https://doi.org/10.2147/CLEP.S148890.
[3] Gosain A, Frykman PK, Cowles RA, Horton J, Levitt M, Rothstein DH, et al. Guidelines for the diagnosis and management of Hirschsprung-associated enterocolitis. Pediatr Surg Int 2017;33(5):517–21. https://doi.org/10.1007/s00383-017-4065-8.
[4] Bernstein CN, Kuenzig ME, Coward S, Nugent Z, Nasr A, El-Matary W, et al. Increased incidence of inflammatory bowel disease after Hirschsprung disease: a population-based cohort study. J Pediatr 2021;233:98–104.e102. https://doi.org/10.1016/j.jpeds.2021.01.060.
[5] Teitelbaum DH, Caniano DA, Qualman SJ. The pathophysiology of Hirschsprung's-associated enterocolitis: importance of histologic correlates. J Pediatr Surg 1989;24(12):1271–7. https://doi.org/10.1016/s0022-3468(89)80566-4.
[6] Levin DN, Marcon MA, Rintala RJ, Jacobson D, Langer JC. Inflammatory bowel disease manifesting after surgical treatment for Hirschsprung disease. J Pediatr Gastroenterol Nutr 2012;55(3):272–7. https://doi.org/10.1097/MPG.0b013e31824f617a.
[7] Nakamura H, Lim T, Puri P. Inflammatory bowel disease in patients with Hirschsprung's disease: a systematic review and meta-analysis. Pediatr Surg Int 2018;34(2):149–54. https://doi.org/10.1007/s00383-017-4182-4.
[8] Lof Granstrom A, Amin L, Arnell H, Wester T. Increased risk of inflammatory bowel disease in a population-based cohort study of patients with Hirschsprung disease. J Pediatr Gastroenterol Nutr 2018;66(3):398–401. https://doi.org/10.1097/MPG.0000000000001732.
[9] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inf 2009;42(2):377–81. https://doi.org/10.1016/j.jbi.2008.08.010.

[10] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inf 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208.
[11] Amiel J, Sproat-Emison E, Garcia-Barcelo M, Lantieri F, Burzynski G, Borrego G, et al. Hirschsprung disease, associated syndromes and genetics: a review. J Med Genet 2008;45(1):1–14. https://doi.org/10.1136/jmg.2007.053959.
[12] Langer JC. Hirschsprung disease. Curr Opin Pediatr 2013;25(3):368–74. https://doi.org/10.1097/MOP.0b013e328360c2a0.
[13] Saberi RA, Gilna GP, Slavin BV, Huerta CT, Ramsey WA, O'Neil Jr CF, et al. Hirschsprung disease in Down syndrome: an opportunity for improvement. J Pediatr Surg 2022;57(6):1040–4. https://doi.org/10.1016/j.jpedsurg.2022.01.065.
[14] Ahmad H, Levitt MA, Yacob D, Halleran DR, Gasior AC, Dilorenzo C, et al. Evaluation and management of persistent problems after surgery for Hirschsprung disease in a child. Curr Gastroenterol Rep 2021;23(11):18. https://doi.org/10.1007/s11894-021-00819-0.
[15] Pruitt LCC, Skarda DE, Rollins MD, Bucher BT. Hirschsprung-associated enterocolitis in children treated at US children's hospitals. J Pediatr Surg 2020;55(3):535–40. https://doi.org/10.1016/j.jpedsurg.2019.10.060.
[16] Dasgupta R, Langer JC. Evaluation and management of persistent problems after surgery for Hirschsprung disease in a child. J Pediatr Gastroenterol Nutr 2008;46(1):13–9. https://doi.org/10.1097/01.mpg.0000304448.69305.28.
[17] Sherman JO, Snyder ME, Weitzman JJ, Jona JZ, Gillis DA, O'Donnell B, et al. A 40-year multinational retrospective study of 880 Swenson procedures. J Pediatr Surg 1989;24(8):833–8. https://doi.org/10.1016/s0022-3468(89)80548-2.
[18] Wolfson S, Whitfield Van Buren K. Very early onset of inflammatory bowel disease in a patient with long-segment hirschsprung's disease. ACG Case Rep J 2020;7(3):e00353. https://doi.org/10.14309/crj.0000000000000353.
[19] Snapper SB. Very-early-onset inflammatory bowel disease. Gastroenterol hepatol (N Y). . 2015;11(8):554–6.
[20] Guariso G, Gasparetto M. Treating children with inflammatory bowel disease: current and new perspectives. World J Gastroenterol 2017;23(30):5469–85. https://doi.org/10.3748/wjg.v23.i30.5469.
[21] Moon JS. Clinical aspects and treatments for pediatric inflammatory bowel diseases. Pediatr Gastroenterol Hepatol Nutr 2019;22(1):50–6. https://doi.org/10.5223/pghn.2019.22.1.50.
[22] Rabizadeh S, Dubinsky M. Update in pediatric inflammatory bowel disease. Rheum Dis Clin N Am 2013;39(4):789–99. https://doi.org/10.1016/j.rdc.2013.03.010.
[23] Rosen MJ, Dhawan A, Saeed SA. Inflammatory bowel disease in children and adolescents. JAMA Pediatr 2015;169(11):1053–60. https://doi.org/10.1001/jamapediatrics.2015.1982.
[24] Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr 2014;58(6):795–806. https://doi.org/10.1097/MPG.0000000000000239.
[25] Hazel K, O'Connor A. Emerging treatments for inflammatory bowel disease. Ther Adv Chronic Dis 2020;11:2040622319899297. https://doi.org/10.1177/2040622319899297.
[26] Cai Z, Wang S, Li J. Treatment of inflammatory bowel disease: a comprehensive review. Front Med (Lausanne) 2021;8:765474. https://doi.org/10.3389/fmed.2021.765474.