OXFORD

Original Article

Long-term Outcomes of Patients Surgically Treated for Hirschsprung Disease

Ahmed Nasr, MD[1,2,3], Viviane Grandpierre, PhD[1], Katrina J. Sullivan, MSc[1], Coralie A. Wong, MSc[4], Eric I. Benchimol, MD, PhD[3,4,5,6,⊕]

[1]Department of Pediatric Surgery, Children's Hospital of Eastern Ontario (CHEO), Ottawa, Ontario, Canada; [2]Department of Surgery, University of Ottawa, Ottawa, Ontario, Canada; [3]CHEO Research Institute, Ottawa, Ontario, Canada; [4]ICES uOttawa, Ottawa, Ontario, Canada; [5]Division of Gastroenterology, Hepatology and Nutrition, CHEO, Ottawa, Ontario, Canada; [6]Department of Pediatrics and School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

Correspondence: Eric I. Benchimol, MD, PhD, FRCPC, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada, e-mail: eric.benchimol@sickkids.ca

Abstract

Background: The only curative treatment for Hirschsprung disease (HD) is surgical repair. However, some patients experience poor postoperative outcomes. We determined long-term outcomes of all HD patients in Ontario, Canada's most populous province.

Methods: We conducted a retrospective cohort study including all children with HD born between April 1, 1991 and March 31, 2014 in Ontario using linked health administrative data. Each HD case was matched to five non-HD controls on sex, date of birth, region of residence and income and followed to March 31, 2016. Chronic diarrhea and constipation were identified using combinations of outpatient physician billing codes in both HD patients and non-HD residents of the province. We determined risk factors associated with diarrhea and constipation, including surgery type and sociodemographic characteristics, using multivariable conditional logistic regression, and reported adjusted odds ratios (aORs).

Results: There were 3,265,172 children born in the study period, of whom 673 had HD. Compared to controls, chronic constipation was more common in HD patients (27.5% versus 2.1%; aOR 17.2, 95% CI 12.6 to 23.4), as was chronic diarrhea (29.9% versus 6.9%, aOR 5.22, 95% CI 4.19 to 6.50). In HD patients, older age at surgery was associated with increased risk of chronic constipation (OR 2.71, 95% CI 1.75 to 4.20). Surgery type, sex, rural/urban residence and income were not associated with risk of chronic constipation or diarrhea.

Conclusion: Chronic constipation and diarrhea were common following surgery for HD. Older age at surgery was associated with subsequent risk of chronic constipation. Surgery type was not associated with increased risk of chronic constipation or diarrhea.

Keywords: *Constipation; Diarrhea; Health administrative data; Hirschsprung disease; Pediatrics; Routinely collected health data; Surgical outcomes*

Background

Hirschsprung disease (HD) is a congenital disorder of the bowel resulting in pathological dysmotility of the colon. While many patients who undergo surgical correction attain satisfactory bowel function, a significant percentage still report poor outcomes (i.e., constipation, diarrhea, impaired continence). Adults who underwent pull-through surgery in infancy report chronic constipation rates between 5% and 33%

(1), and mild-to-severe diarrhea in 54.8% of patients (2). Fecal soiling and fecal incontinence are also common outcomes of pull-through surgery, affecting up to 48% of patients (1). Bowel function tends to improve from childhood to adolescence (3,4); however, during adulthood, increasing age is associated with greater impairment in bowel function. Overall, approximately 50% of adults with a history of HD report chronic bowel dysfunction (1,5) and few population-based studies have investigated long-term bowel function of HD (6). The aim of this study was to conduct a population-based assessment of long-term bowel function outcomes, defined as chronic constipation and diarrhea, after pull-through surgery for HD in Ontario, Canada's most populous province. In addition, we determined whether sociodemographic characteristics and surgical technique were associated with increased risk of chronic constipation and chronic diarrhea.

METHODS

This study was approved by the Research Ethics Board of Children's Hospital of Eastern Ontario (12/147X).

Study Design, Setting and Data Sources

This population-based cohort study used health administrative data from Ontario, Canada (population 13.4 million people, 38% of the Canadian population) (7). Ontario collects health administrative data on all legal residents who qualify for universal single-payer healthcare (>99% of the population). Data are maintained by ICES via an agreement with the Ontario Ministry of Health and Long-Term Care, with the data available to researchers in uncleaned and unedited format (8). The authors had full access to the uncleaned data. Multiple databases are linked deterministically using a unique encrypted identification number based on the Ontario health card number assigned to each Ontario resident.

We used the followed databases for the current study: (i) Registered Persons Database (RPDB) that includes date of birth, postal code of residence, and updated information on vital status and migration out of Ontario; (ii) Ontario Health Insurance Plan (OHIP) data that includes physician billing data since 1991 using a simplified three-digit version of International Classification of Diseases (ICD), ninth edition (ICD-9); (iii) National Ambulatory Care Reporting System for emergency department visits from 2002 onward using the ICD-10 classification system; and (iv) Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) containing medical hospitalizations since 1988 using the ICD-9 classification system until 2002, and the ICD-10 classification system from 2002 onward. We used the MOMBABY data file to identify live births, which uses information from CIHI-DAD and links the health records of mothers with those of their newborns for all Ontario hospital births (>98% of births in Ontario) (9).

Study Population

To identify children born with HD between fiscal years (FY) 1991 to 2013 (April 1, 1991 to March 31, 2014), we used a previously validated algorithm, which relied on the presence of a hospitalization with diagnostic code for HD, plus a surgical or biopsy code for HD-related procedure. This identified patients with HD from within Ontario health administrative data with the following diagnostic accuracy: sensitivity 93.5%, specificity >99.9%, positive predictive value 89.6% and negative predictive value >99.9% (10).

All children born in Ontario during the same period without HD were considered to be controls. Each HD case was matched to five controls on sex, date of birth (±90 days), region of residence based on Local Health Integration Network (regional administrative structure of the Ontario health system) and mean neighbourhood income quintile (a validated proxy for individual-level income) (8). Cases and controls were followed to when they died, left the province or until March 31, 2016.

We excluded cases and controls who did not have continuous OHIP eligibility from birth to the date of the HD corrective surgery, who lost OHIP eligibility before their first birthday or who moved out and then back into the province (and therefore had discontinuous records in the databases).

Outcomes

To determine the long-term outcomes of HD patients and controls, the OHIP database was searched for physician visits associated with diagnostic codes for diarrhea (009) or constipation (564). Patients with chronic diarrhea and chronic constipation were defined as those with three or more physician visits associated with those diagnostic codes, spaced ≥4 weeks apart, within 1 year.

Predictor Variables

Surgery type and date were defined as the procedures contained within the CIHI-DAD. These procedures were coded using the Canadian Classification of Health Interventions (CCI) (prior to April 1, 2002) and the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) (on/after April 1, 2002) systems. However, since Duhamel and Soave procedures were not coded separately after FY 2002, we determined the association between surgery type and outcome only for patients who were born and underwent surgery between FY 1991 and 2001 (i.e., April 1, 1991 to March 31, 2002). Long-term outcomes were compared between the groups including sociodemographic.

Statistical Analysis

Descriptive characteristics were reported as proportions, or means (±SD) or medians (with interquartile range) where appropriate. Rates of chronic diarrhea and constipation (associated with outpatient physician visits) were compared

between HD patients and all non-HD residents of the province and reported as proportions. Kaplan–Meier survival curves demonstrated time to diagnosis with chronic constipation and diarrhea. Data were censored at end of study period, death or migration out of the province. To determine the association between predictor variables with outcomes, we used a conditional logistic regression analysis to compare HD patients (diagnosed 1991 to 2001) to matched controls. For these predictive models, patients who did not undergo surgery were excluded. Results are presented as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). *P* value of <0.05 were considered statistically significant. Analyses were conducted with SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Descriptive Characteristics

Of the 3,265,172 Ontario children born in the study period, 673 (0.02%) were diagnosed with HD. The majority of HD patients were male (75.3%), and lived in an urban setting at the time of diagnosis (86.8%). There was almost an equal number who underwent Soave and Duhamel procedures (33.2% versus 29.5%). Table 1 provides an overview of the patient characteristics.

Outcomes

Incidence of chronic constipation was significantly higher in HD patients compared to controls (27.5% versus 2.1%, aOR 17.2, 95% CI 12.6 to 23.4), as was chronic diarrhea (29.9% versus 6.9%, aOR 5.22, 95% CI 4.19 to 6.50). Survival curves showing time-to-event for HD and non-HD are presented in Figures 1 and 2.

Predictors of Outcomes

Of the 344 HD patients diagnosed from FY1991 to 2001, 292 (84.9%) had a record of surgical correction. Surgery type, sex, rural/urban residence and income were not associated with odds of chronic constipation or diarrhea. However, older age at surgery was associated with increased odds of chronic constipation (OR 2.71, 95% CI 1.75 to 4.20) (Table 2).

Discussion

This is the first population-based study to examine the long-term risk of chronic constipation and diarrhea in children with HD. We found a significantly higher risk of these conditions in children with HD compared to non-HD controls. The only predictor of chronic constipation in these patients was older age at

Table 1. Descriptive characteristics of patients with HD and the non-HD population

Characteristics, N (%)	HD (n = 673)	Non-HD (n = 3,264,499)
Sex		
Female (%)	166 (24.7%)	1,589,061 (48.7%)
Mean age at surgery, year (±SD)	0.26 ± 1.16	NA
Era of diagnosis, n (%)		
1991–2001	344 (51.1%)	NA
2002–2013	329 (48.9%)	
Mean follow-up time from birth, year ± SD	13.7 ± 6.6	13.4 ± 6.7
Intervention (pre-2002 only), n = 344		
Soave	97 (33.2%)	
Duhamel	86 (29.5%)	NA
Other/Swenson	109 (37.3%)	
None/missing	52 (15.1%)	
Income quintile		
1	152 (22.6%)	748,967 (22.9%)
2	147 (21.8%)	656,765 (20.1%)
3	126 (18.7%)	643,638 (19.7%)
4	139 (20.7%)	645,061 (19.8%)
5	105 (15.6%)	526,306 (16.1%)
Missing	4 (0.6%)	43,762 (1.3%)
Household at diagnosis		
Rural	86 (12.7%)	385,672 (11.8%)
Urban	589 (86.8%)	2,856,327 (87.5%)
Missing	4 (0.6%)	22,500 (0.7%)

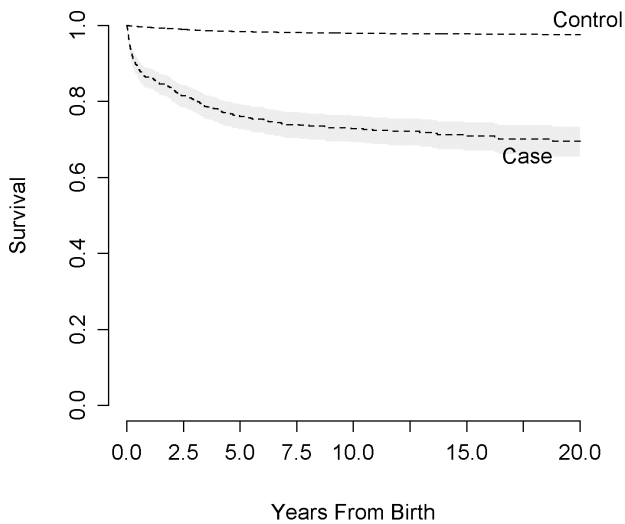HD, Hirschsprung disease; NA, not applicable.

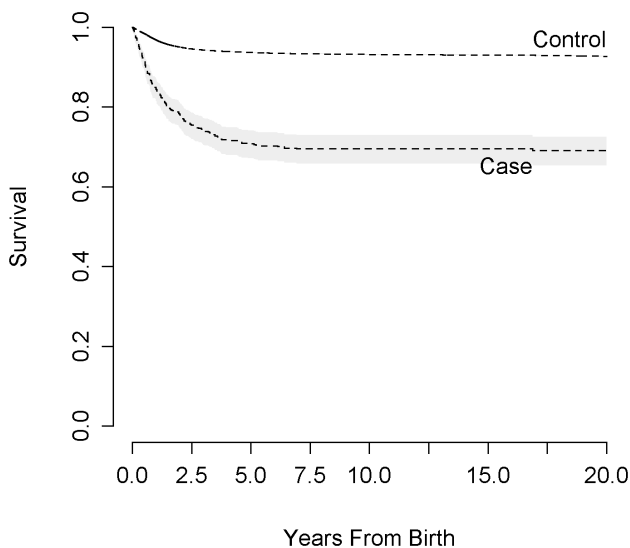**Figure 1.** Time to diagnosis with chronic constipation.

Figure 2. Time to diagnosis with chronic diarrhea.

surgical correction of the HD. Sociodemographic characteristics and surgical technique were not associated either chronic constipation or diarrhea.

The finding that HD patients were at greatly increased risk for chronic constipation and diarrhea is not surprising given poor postoperative bowel function outcomes in these patients described by other investigators (1,2). It has been well documented that although HD patients achieve reasonably satisfactory bowel function after surgery, but many continue to experience long-term complications, such as constipation, diarrhea and fecal incontinence (3,11–17). In our cohort, we noted that chronic diarrhea tended to occur by 5 years of age, with the likelihood of new diagnoses levelling off thereafter (Figure 2). However, new-onset chronic constipation seemed to continue to occur at a gradual rate after 5 years of age, to the maximum

follow-up of 20 years from birth (as demonstrated in Figure 1). Existing literature suggests these complications can significantly impair a child's quality of life. For example, in a cohort of post-pull-through HD children aged 5 to 15, 50% reported that their bowel function had a significant negative effect on their activities and social lives (4,18). Specifically, HD children reported limitations in physical activities, social interactions and food intake, as well as decreased school attendance, due to their bowel symptoms (5,17). Examining type of surgical procedure revealed no significant association between surgery type and bowel function outcome; however, there appears to be varying reports that either support this finding (16,19,20) or refute it (21). It should be noted that the latter study compared modified procedures (e.g., transanal endorectal pull-through and the Soave procedures) and found incontinence and bowel movement frequency to be significantly lower in patients who had undergone the transanal endorectal pull-through procedure.

In our study, only older age at surgery was associated with increased risk of chronic constipation. Another study investigating quality of life in HD patients reported overflow incontinence was less severe in children who had pull-through surgery at an earlier age (22), lending support to our finding that delayed surgical intervention can lead to poorer long-term bowel function. Langer (23) explained delayed diagnosis of HD (thereby delayed intervention) typically leads to increased thickening and dilatation of the colon, the presence of which requires surgeons performing transanal dissection to excessively stretch the anal sphincter. This can lead to long-term bowel function issues.

Limitations

The use of health administrative data allows for a population-based assessment of outcomes in a large population of HD patients. As with any study using health administrative data, there is the risk of misclassification bias associated with the use of physician billing, hospitalization and surgical codes to identify patients and outcomes. However, we used a validated algorithm to identify patients with HD (6). The unusual finding of 15% of HD patients not receiving corrective surgery prior to 2002 (and 12.7% overall) may be attributed to misclassification bias (surgery was incorrectly coded within hospitalization data), or may be due to milder, short-segment HD for which surgery was not necessary. The algorithms used to identify the outcomes of chronic constipation and chronic diarrhea were established by the expert clinicians in our group (AN and EIB), but have not been validated. Unfortunately, the lack of granularity in the diagnostic codes associated with outpatient physician billing (which used a simplified three-digit ICD-9 scheme) did not allow us to distinguish diarrhea from fecal incontinence. There is no reason to believe these algorithms differentially identify the outcomes in patients

Table 2. Regression analysis to determine influence of type of surgery on long-term outcomes

Outcome	Effect	Level	Adjusted odds ratio (95% confidence interval)	P-value
Diarrhea	Surgery	Duhamel	0.99 (0.54–1.81)	0.97
		Other/Swenson	0.64 (0.35–1.17)	0.15
		Soave	Ref.	Ref.
	Age at surgery (years)		1.00 (0.72–1.39)	0.98
	Sex	Male	1.25 (0.67–2.35)	0.48
		Female	Ref.	Ref.
	Household	Rural	0.69 (0.35–1.367)	0.29
		Urban	Ref.	Ref.
	Income quintile	1 (lowest)	0.99 (0.43–2.25)	0.97
		2	1.22 (0.54–2.76)	0.64
		3	1.01 (0.43–2.40)	0.98
		4	0.71 (0.29–1.74)	0.45
		5 (highest)	Ref.	Ref.
Constipation	Surgery	Duhamel	1.05 (0.52–2.10)	0.89
		Other/Swenson	1.65 (0.87–3.14)	0.13
		Soave	Ref.	Ref.
	Age at surgery (years)		2.71 (1.75–4.20)	<0.0001
	Sex	Male	1.20 (0.61–2.35)	0.60
		Female	Ref.	Ref.
	Household	Rural	1.23 (0.61–2.46)	0.56
		Urban	Ref.	Ref.
	Income quintile	1 (lowest)	1.69 (0.64–4.42)	0.29
		2	2.03 (0.78–5.29)	0.15
		3	1.04 (0.37–2.94)	0.95
		4	2.45 (0.92–6.51)	0.07
		5 (highest)	Ref.	Ref.

Ref. Reference.

with HD compared to the general population. Therefore, ascertainment bias is unlikely.

Additionally, the population-based data in this study did not allow for more nuanced questions regarding predictive factors of outcomes such as length of aganglionic segment, presence of dilated upstream bowel, pathologic findings (transition-zone pull-through, etc.). Nonetheless, the data still provided results indicating older age at surgery was associated with subsequent risk of chronic constipation, and also found no association that surgery type increased risk of chronic constipation or diarrhea.

Ontario has a universal health care system whereby necessary medical costs of legal residents are covered by the provincial government. This may explain why sociodemographic characteristics such as rural/urban residence and income did not impact outcomes of the patients with HD. This finding may not hold true in other regions of the world, where access to care may present a challenge. Of note, we did not determine the burden of diarrhea or constipation on the patient or health system after the initial diagnosis, nor did we assess whether these symptoms resolved with time. These questions will be addressed in future research.

Conclusions

This study sought to determine the risk of chronic bowel dysfunction in patients with HD, compared to general population controls. We found that HD patients were at far greater risk of chronic constipation and chronic diarrhea compared to non-HD controls. The risk of chronic constipation was greater in children who underwent pull-through surgery at an older age, but surgical method and sociodemographic characteristics were not associated with bowel dysfunction. Further research should strive to identify patients and risk for long-term bowel dysfunction in order to improve the outcomes of children with HD.

Funding

Acknowledgements

Conflicts of Interest: EB is an Associate Editor of the *Journal of the Canadian Association of Gastroenterology*. All other authors declare no conflicts of interest.

Author Contributions: Study conception and design: EIB and AN; data acquisition: CAW and KJS; analysis and data interpretation: EIB, AN and VG; drafting of the manuscript: EIB, AN and VG; critical revision of the manuscript: EIB, AN, KJS and VG; final approval of the manuscript; EIB, AN, VG, KJS and CAW.

References

1. Rintala RJ, Pakarinen MP. Long-term outcomes of Hirschsprung's disease. Semin Pediatr Surg 2012;21(4):336–43.
2. Ieiri S, Nakatsuji T, Akiyoshi J, et al. Long-term outcomes and the quality of life of Hirschsprung disease in adolescents who have reached 18 years or older—a 47-year single-institute experience. J Pediatr Surg 2010;45(12):2398–402.
3. Niramis R, Watanatittan S, et al. Quality of life of patients with Hirschsprung's disease at 5–20 years post pull-through operations. Eur J Pediatr Surg 2008;18(1):38–43.
4. Yanchar NL, Soucy P. Long-term outcome after Hirschsprung's disease: Patients' perspectives. J Pediatr Surg 1999;34(7):1152–60.
5. Bai Y, Chen H, Hao J, et al. Long-term outcome and quality of life after the Swenson procedure for Hirschsprung's disease. J Pediatr Surg 2002;37(4):639–42.
6. Neuvonen MI, Kyrklund K, Lindahl HG, et al. A population-based, complete follow-up of 146 consecutive patients after transanal mucosectomy for Hirschsprung disease. J Pediatr Surg 2015;50(10):1653–8.
7. Population and Dwelling Counts, for Canada, Provinces and Territories, 2016 and 2011 Censuses. Ottawa, Ontario, Canada: Statistics Canada, 2016. <http://www12.statcan.gc.ca/census-recensement/2016/dp-pd/hlt-fst/pd-pl/Table.cfm?Lang=Eng&T=101&S=50&O=A> (updated February 20, 2019; Accessed July 1, 2020).
8. ICES Data Dictionary. Updated version 3.0.12. Toronto, Ontario, Canada: ICES, 2020. <https://datadictionary.ices.on.ca/> (Accessed July 1, 2020).
9. Maaten S, Guttman A, Kopp A, Handa M, Jaakkimainen L. Care of women during pregnancy and childbirth. In: Jaakkimainen L, ed. Primary Care in Ontario ICES Atlas. Toronto, Ontario, Canada: Institute for Clinical Evaluative Sciences, 2006.
10. Nasr A, Sullivan KJ, Chan EW, et al. 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.
11. Moore SW, Albertyn R, Cywes S. Clinical outcome and long-term quality of life after surgical correction of Hirschsprung's disease. J Pediatr Surg 1996;31(11):1496–502.
12. Engum SA, Grosfeld JL. Long-term results of treatment of Hirschsprung's disease. Semin Pediatr Surg 2004;13(4):273–85.
13. Marty TL, Seo T, Matlak ME, et al. Gastrointestinal function after surgical correction of Hirschsprung's disease: Long-term follow-up in 135 patients. J Pediatr Surg 1995;30(5):655–8.
14. Aworanti OM, Mcdowell DT, Martin IM, et al. Comparative review of functional outcomes post surgery for Hirschsprung's disease utilizing the paediatric incontinence and constipation scoring system. Pediatr Surg Int 2012;28(11):1071–8.
15. 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.
16. Zhang SC, Bai YZ, Wang W, et al. Long-term outcome, colonic motility, and sphincter performance after Swenson's procedure for Hirschsprung's disease: A single-center 2-decade experience with 346 cases. Am J Surg 2007;194(1):40–7.
17. Catto-Smith AG, Trajanovska M, Taylor RG. Long-term continence after surgery for Hirschsprung's disease. J Gastroenterol Hepatol. 2007;22(12):2273–82.
18. Sood S, Lim R, Collins L, et al. The long-term quality of life outcomes in adolescents with Hirschsprung disease. J Pediatr Surg 2018;53(12):2430–4.
19. Nasr A, Haricharan RN, Gamarnik J, Langer JC. Transanal pullthrough for Hirschsprung disease: Matched case–control comparison of Soave and Swenson techniques. J Pediatr Surg 2014;49(5):774–6.
20. Khazdouz M, Sezavar M, Imani B, et al. Clinical outcome and bowel function after surgical treatment in Hirschsprung's disease. Afr J Paediatr Surg 2015;12(2):143–7.
21. Onishi S, Nakame K, Yamada K, et al. Long-term outcome of bowel function for 110 consecutive cases of Hirschsprung's disease: Comparison of the abdominal approach with transanal approach more than 30 years in a single institution—is the transanal approach truly beneficial for bowel function? J Pediatr Surg 2016;51(12):2010–4.
22. Khalil M. Long-term health-related quality of life for patients with Hirschsprung's disease at 5 years after transanal endorectal pull-through operation. Qual Life Res 2015;24(11):2733–8.
23. Langer JC. Laparoscopic and transanal pull-through for Hirschsprung disease. Semin Pediatr Surg 2012;21(4):283–90.