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Impaired Growth Outcomes in Children with Congenital Colorectal Diseases

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Abstract

Purpose—Cloaca, Hirschsprung disease, and Anorectal Malformations (CHARM) are congenital anomalies of the hindgut. Small series have suggested that children suffering from one of these anomalies may be at risk for growth impairment. We sought to expand on these findings in a comprehensive cohort, hypothesizing that patients with Medicaid Insurance or African American (AA) race would be at higher risk for poor growth.

Methods—Following IRB approval, single-institution retrospective review of children with CHARM anomalies was performed (2009–2016). Body Mass Index (BMI) value Z-scores were obtained using the 2006 World Health Organization (age 0–24 months) and 2000 Centers for Disease Control (age >2 years) growth charts and calculators (SAS). Patient factors and BMI Z-scores were analyzed with descriptive statistics and Fisher's exact test.

Results—166 patients (Cloaca n=16, HD n=71, ARM n=79) were identified. The BMI Z-score distribution for the entire CHARM cohort was lower than controls ($p<.0001$). HD and ARM BMI Z-scores were also lower vs. controls ($p<.0007$, $p<.0037$). Requiring more or less than the average number of surgeries did not impact BMI Z-score ($p=NS$). Patients with Medicaid had lower Z-scores vs. Private or Commercial insurance ($p<.0001$). AA race BMI z-score distribution was

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Conflict of Interest

No conflict of interest.

Author Contributions

Study conception and design: PNC, AG

Acquisition of data: LVV, PNC, AZT, AG

Analysis and interpretation of data: LVV, PNC, AZT, AG

Drafting of manuscript: LVV, AG

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lower than controls ($p<.0002$), but there was no statistical difference in BMI z-scores when comparing African-American vs. non-African-American CHARM patients ($p=NS$).

Conclusions—Patients born with CHARM anomalies are at risk for impaired growth. Further study is warranted to identify modifiable risk factors contributing to this impairment. Longitudinal follow-up should include interventions to mitigate these risks.

Keywords

Cloaca; Hirschsprung; Anorectal malformation; Growth; Development; Congenital

Introduction

Cloaca, Hirschsprung disease, and Anorectal Malformations (CHARM) are a diverse group of complex congenital malformations involving the lower gastrointestinal tract. They constitute the most common hindgut anomalies in the newborn with an estimated cumulative incidence of approximately 40.3 per 100,000 live births.^{1–3} There are no known differences in the incidences of these anomalies among different races or socioeconomic status. However, disparities in surgical treatment allocation, resource utilization, and long-term outcomes have been preliminarily identified as a function of primary payer status and patient race.⁴ Demographic analyses have suggested that lower socioeconomic status and minority race may be associated with delayed recognition of pediatric surgical conditions, higher incidence of urgent and emergent procedures, increased length of hospital stay, as well as limited access to care and referral to specialized centers.^{4,5}

Moreover, growth in the first two years of life has been shown to predict neurodevelopmental outcomes.^{7,8} Children born with anomalies of the gastrointestinal tract exhibit suboptimal weight gain during the first year of life.⁹ In addition, neonates who undergo surgery for both cardiac and non-cardiac anomalies have cognitive and motor delay.^{10,11} A number of factors may predispose children suffering from these anomalies to marked and persistent growth and developmental compromise. However, to date only a handful of studies have reported long-term growth outcomes in patients with individual CHARM anomalies.^{1,2,12} Overall, these show trends towards impaired growth and raise concern for potential poor developmental consequences.

The aims of the current study were to 1) describe the long-term growth outcomes of a cohort of children with CHARM anomalies, and 2) investigate the impact of potentially modifiable risk factors for poor long-term growth outcomes. We hypothesized that children with CHARM anomalies suffer from long-term growth impairment compared to the general population. We further hypothesized that patients with Medicaid insurance, African American race, and/or associated congenital anomalies are at greater risk for compromised growth.

Methods

Patient Identification and data extraction

This study was approved by The University of Tennessee Health Science Center Institutional Review Board. A single-institution retrospective review of pediatric patients with cloaca, Hirschsprung disease (HD) and Anorectal Malformation (ARM) (collectively CHARM) anomalies between 2009–2016 was performed. The initial cohort was identified using ICD-9 and ICD-10 codes for CHARM anomalies (42.3, 43.6, 751.2, 751.3, 751.5). Confirmation of anomaly type was performed by individual chart review. Patients were excluded if their index operation took place at an outside institution or if operative details were unavailable for review. Data were extracted from the Electronic Medical Record: diagnosis, race, ethnicity, height, weight, Body Mass Index (BMI) when available, length of stay and primary insurance for each patient encounter. Information regarding number of surgical interventions and number and type of congenital anomalies was obtained through individual chart review.

Body Mass Index Calculations and Statistical Analyses

When BMI was not available for an encounter, it was calculated using height and weight only when these were recorded either together or within a two-week period. Normal BMI values and BMI comparisons were calculated in Statistical Analysis System (SAS) using the 2006 World Health Organization Growth Chart Calculator for children between 0 and 24 months and the 2000 Centers for Disease Control Growth Chart Calculator for children 2 years or greater.^{13,14} These programs were also used to identify implausible BMI values. These programs provide a BMI z-score, which is the number of standard deviations above or below the population mean value for each observation. CDC data is derived from several national health surveys, while WHO data is derived from international health data which includes the United States.^{13,14}

Demographics, BMI, and surgical history were analyzed with descriptive statistics and Fisher's exact test. Follow-up times were compared with analysis of variance. A p-value of <0.05 was considered statistically significant. All analyses were performed using SAS® version 9.4 (Cary, NC).

Results

Demographics

166 patients (Cloaca n=16, HD n=71, ARM n=79) were identified. The majority were males (64%) and had ARM (48%, Table 1). Patients with cloaca underwent more surgical interventions and spent more time in the hospital in the first year of life than patients with HD or ARM. Mean follow-up time was significantly higher in both the cloaca (7.2 yr. +/- 3.7, p=.0005) and HD (6.6 yr. +/- 3.3, p<.0001) cohorts compared to ARM (4.6 yr. +/- 2.3). Half of the patients had at least one associated congenital anomaly (Table 2); the most common organ systems involved were cardiac, skeletal, and urogenital. Patients with HD had fewer associated congenital anomalies (18%) compared to ARM (67%) and cloaca (100%), p<.0001.

Growth curves and Z-score distributions

The growth curves for each anomaly type and age category are shown in Figure 1. The BMI z-score distribution for the collective CHARM cohort was lower than controls (median z-score -0.409 , $p<.0001$). When examining individual anomalies, HD and ARM BMI z-scores were also lower vs. controls ($p<.0009$, $p<.0037$, Table 3). However, the sample size for cloaca ($n=16$) was too small to achieve statistical significance. Within the ARM cohort, there was no difference in BMI z-scores for males versus females. Gender differences could not be tested in cloaca and HD due to skewed gender distributions in those groups. Undergoing greater than versus less than the average number of surgeries did not impact BMI z-score ($p=NS$).

Disparities

CHARM patients of African-American race had a BMI z-score distribution which was lower than controls (median z-score -0.765 , $p<.0002$). This difference persisted when comparing only ARM African-American patients to controls (median z-score -1.109 , $p=0.0065$, Table 4). African-American patients with HD were not found to have lower z-score distributions ($p=NS$). There were not enough African-American cloaca patients in this series to test this hypothesis. Patients with Medicaid were found to have a significantly lower z-score distribution versus Private or Commercial insurance ($p<.0001$, Table 5).

Discussion

Our study comparing the three CHARM populations over a seven-year period demonstrated that patients with these anomalies have significantly lower BMI z-scores than normal children. We did not identify differences in growth outcomes when comparing the three sub-groups. This suggests a common risk factor or set of risk factors for growth impairment. In our population, African-American race was associated with lower BMI than the general population, but did not have an effect on growth outcomes within the CHARM cohort. Additionally, we did identify significantly lower BMI z-scores in patients with Medicaid as their primary insurance compared to private or commercial forms of insurance. To our knowledge, this is the first study to identify racial and socioeconomic disparities in children with CHARM anomalies.

In a retrospective study of 62 patients with cloacal exstrophy, Fullerton et al. also reported substantial height and weight deficits compared to the general population.¹² Despite this finding, BMI was not significantly affected. In their patient cohort, short bowel syndrome and enterocystoplasty were associated with adversely affected growth. In a prospective study of non-syndromic children with ARM in the Netherlands, van den Hondel et al. demonstrated significantly lower height through five years of age and significantly lower weight-for-height until two years of age compared to the normative population.² The type of malformation did not significantly affect growth parameters. However, in their series, the presence of additional anomalies was associated with significantly impaired growth. Physical growth outcomes in Hirschsprung's disease are more variable in the literature, although generally more favorable than those reported for other CHARM anomalies. In a retrospective follow-up study of infants with HSCR in Australia, More et al. found no

significant height or weight deficits compared to the general population; however height percentile at one year of age was significantly lower than at birth.¹ In a long-term follow up study of patients with total colonic aganglionosis, 25% of patients at 5 years, 20% of patients at 10 years, and 63% of patients at 15 years of age were below the second percentile for body weight.¹⁵ Compromised growth in congenital colorectal disease is likely of multifactorial origin, highlighting the need for a multidisciplinary approach to improving outcomes.

Patients with CHARM anomalies frequently have major systemic comorbidities implicated in growth impairment, including concomitant congenital anomalies and genetic syndromes, which are reported in up to 87% of cloaca, 46% of ARM, and 30% of HSCR patients.^{2,12,16} Short bowel syndrome and the absence of a functional colon commonly lead to micronutrient and total body sodium deficits, respectively, that adversely affect growth.^{12,17} Metabolic acidosis resulting from urinary diversion and related gastrointestinal losses has been shown to contribute to perturbed calcium homeostasis and metabolic bone disease as well as a blunted growth hormone axis, particularly in patients with cloacal exstrophy who often have renal insufficiency.^{12,18,19} Recalcitrant gastrointestinal issues such as constipation, incontinence, and enterocolitis are common following surgical reconstruction and may result in chronic malnutrition, recurrent hospital admissions, and multiple operations.^{20–22} Additionally, the Centers for Medicare and Medicaid currently limit Medicaid coverage of major surgical procedures to 90 days under the global surgery package.⁶ While our study was not designed to assess adequacy of longitudinal follow-up, the sparsity of available data at longer-term follow-up times suggests that limited extended postoperative follow-up care could contribute to poor growth outcomes in these patient populations.

The relatively large sample size of our cohort and the follow-up time included were the principal strengths of this study. Additionally, our use of WHO and CDC guides for calculating BMI, in contrast to reporting height and weight alone, allowed for a more accurate comparison to the general population. However, these guides represent optimal growth and may not be reflective of the local population, which may theoretically differ from the general populations represented in the growth curves. As with all retrospective studies, we were limited in the availability of complete data for each patient. Particularly after the neonatal period, measurements of height and weight became increasingly sparse. One area we did not explore in this study was frequency and duration of parenteral nutrition, which may have a role in patients suffering from acute and/or chronic malnutrition related to their disease process and multiple hospital admissions. However, now that we have identified certain risk factors based on our population, future study can expand to include additional modifiable and non-modifiable characteristics.

Conclusions

Patients with CHARM anomalies who are of African-American race or low socioeconomic status are at risk for poor growth outcomes. However, whether race, socioeconomic status, or the anomaly itself plays the largest role in delaying growth is still unknown. Further research is needed to identify modifiable risk factors for growth and interventions to mitigate these

risks. A multi-institutional collaboration will be beneficial in studying this at-risk population.

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Figure 1. Growth Charts

(A) World Health Organization growth curves for median BMI per encounter for children 0–2 years with Cloaca. (B) Centers for Disease Control growth curves for median BMI per encounter for children 2–20 years with Cloaca. (C) World Health Organization growth curves for median BMI per encounter for children 0–2 years with Hirschsprung disease. (D) Centers for Disease Control growth curves for median BMI per encounter for children 2–20 years with Hirschsprung disease. (E) World Health Organization growth curves for median BMI per encounter for children 0–2 years with Anorectal Malformations. (F) Centers for

Disease Control growth curves for median BMI per encounter for children 2–20 years with Anorectal Malformations.

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Table 1

Demographics.

	Cloaca (n=16)	ARM (n=79)	HD (n=71)	p-value
Gender (n, %)				<0.0001
Female	14 (87.5)	36 (45.6)	9 (12.7)	
Male	2 (12.5)	43 (54.4)	62 (87.3)	
Race (%)				0.1060
Hispanic/Latino	12.5	7.6	7	
Non-Hispanic White	31.25	45.6	33.8	
Non-Hispanic Black/AA	56.25	40.5	59.2	
Other	0	6.3	0	
Insurance (%)				0.7038
Commercial	0	11.4	12.7	
Government	87.5	83.5	78.9	
Private Pay	0	1.3	1.4	
Unknown	12.5	3.8	7.0	
Congenital anomalies (%)	100	67	18	
Median # surgeries (IQR)	4.5 (3–7.5)	2 (1–4)	3 (2–5)	
Median # inpatient days in first year of life (IQR)	89.3 (35.4–162.2)	15.6 (10.8–28.8)	34.1 (24.4–40.8)	
Mean follow-up time (yr.)	7.2	4.6	6.6	

Table 2

Associated congenital anomalies.

	Cloaca (n=16)	Hirschsprung (n=71)	ARM (n=78)
Pulmonary	1	0	0
Skeletal	10	1	28
Urogenital	14	5	22
Cardiac	7	9	34
GI	9	2	9
CNS	7	1	12
Total	16 (100%)	13 (18.3%)	53 (67.1%)

Table 3

BMI Z-score distribution in CHARM patients.

Group	N	Mean	Standard Deviation	95% CI for Mean estimate	Lower Quartile	Median	Upper Quartile	p-value
Cloaca	14	-0.084	1.519	-0.9613 – 0.7931	-0.887	-0.018	0.619	0.8390
Hirschsprung	66	-0.380	1.442	-0.7342 – 0.0251	-1.382	-0.388	0.594	0.0363
ARM	76	-0.513	1.655	-0.8912 – 0.1350	-1.701	-0.407	0.576	0.0085

Table 4

BMI Z-score distribution for African-American CHARM patients.

Group	Mean	SD	95% CI for Mean estimate	Lower Quartile	Median	Upper Quartile	p-value
Cloaca (n=7)	0.036	1.835	-1.6605 – 1.7329	-1.566	-0.041	2.256	<i>ref</i>
Hirschsprung (n=39)	-0.301	1.427	-0.7630 – 0.1618	-1.382	-0.057	0.594	0.1960
ARM (n=31)	-0.886	1.687	-1.5047 – 0.2674	-2.225	-1.109	0.169	0.0065

Table 5

BMI Z-score distributions by insurance type.

Group	Insurance	Minimum	Lower Quartile	Median	Upper Quartile	Maximum	p-value
ARM	Commercial (n=9)	-2.418	0.088	0.331	0.855	2.137	-----
	Government (n=66)	-4.647	-1.753	-0.548	0.564	3.089	0.0061
	Private Pay/Uninsur ed (n=1)	-0.976	-0.976	-0.976	-0.976	-0.976	-----
Cloaca	Government (n=14)	-2.684	-0.887	-0.018	0.619	2.668	-----
Hirschsprung	Commercial (n=9)	-1.889	-1.150	-1.010	0.594	1.202	-----
	Government (n=56)	-4.189	-1.402	-0.252	0.595	2.654	0.0718
	Private Pay/Uninsur ed (n=1)	-0.574	-0.574	-0.574	-0.574	-0.574	-----