Original Article

Long-term impact of fistula status on growth and anemia in infants with congenital anorectal malformations

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Background and Objectives: To evaluate the impacts of fistula status over 12 months on growth and development and anemia in infants with anorectal malformation (ARM) and to analyze the effects of comorbidities. **Methods and Study Design:** The ARM group included infants who suffered from ARM and underwent three operations including colostomy, anoplasty (group A) and fistula closure (group B). The normal group included infants aged approximately 6 months and 12 months who were classified as groups C and D. A 24-h dietary recall questionnaire was completed by the guardians of all the participants. Data on height, weight, hemoglobin (Hb) level and comorbidities were extracted from electronic medical records. Then, we compared the impacts of the 12-month fistula status on growth and development and anemia among the infants. **Results:** In total, 47 patients in the ARM group and 100 infants in the normal group were included. The height-for-age z-score (HAZ) was lower in group A than in group B. Compared with those in group D, weight, height, the HAZ and the weight-for-age z-score (WAZ) were lower in group B. The incidence of anemia was higher in the ARM group than in the normal group. **Conclusions:** Patients with ARM are at risk for growth problems and anemia. The long-term impacts of fistula status on infant length presented earlier than those associated with other physical indicators. Compared to infants with urogenital comorbidities, those with congenital heart disease (CHD) seemed to be more prone to growth disorders and anemia.

Key Words: congenital anorectal malformation, growth, infant, anemia

INTRODUCTION

Congenital anorectal malformations (ARMs) are the most common gastrointestinal malformations, with an incidence of 1/5000 newborns.[1] For infants with ARMs in China, treatment comprises three operations: colostomy (in newborns), anoplasty (in infants nearly 6 months old) and fistula closure (in infants nearly 1 year old). With the development of surgical techniques, the curative effect in patients has improved. It has been reported that infants with ARM suffer from postoperative dysphoria,[2,3] poor quality of life and psychosocial developmental disorders.[4,5] Because of frequent hospital admissions and comorbidities in early life, it has been suggested that infants suffering from ARM may be at risk for growth impairment. Nonetheless, data on the long-term impact of fistula status on infant growth remain controversial. A study showed that over 75.9% of infants who underwent ostomy (76.7% with colostomy included) experienced eutrophia according to analyses of indicators including the HAZ, WAZ, and BMI z-score (BAZ).[6] However, other studies reported that malnutrition was obvious during the enterostomy period, and the time of enterostomy tube placement in infants with a persistent growth problem was prolonged.[1] Minutillo showed that infants born with gastrointestinal abnormalities exhibited suboptimal weight gain in the first year of life.[7] It was indicated that growth and development in the first two years of life can predict neurodevelopmental outcomes.[8,9] To date, only a handful of studies have reported long-term growth outcomes in patients with ARM.[1,10,11]

Anemia is a major health concern, especially in developing countries. The most vulnerable groups are pregnant women, infants, and children. For infants with ARM,

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several types of surgical interventions and poor dietary intake in early life lead to poor health outcomes. The incidence of anemia in infants with ARM is unknown.

One of the aims of this study was to evaluate the impact of the 12-month fistula status on growth and anemia in infants with ARM and to analyze the effects of comorbidities. Moreover, this study aimed to compare growth and development and the prevalence of anemia between the ARM group and the normal group.

METHODS

Patients, inclusion, and exclusion

The study was designed as a retrospective study with 2 groups. The ARM group included infants with ARM who received three operations including colostomy (in newborns),[2] anoplasty (in infants approximately 6 months old) and fistula closure (in infants approximately 1 year old) from January 2017 to December 2019. In the ARM group, infants who underwent anoplasty and fistula closure were defined as group A and group B, respectively. In the normal group, infants randomly selected from the Department of Child Health Care who were aged approximately 6 months and 12 months were assigned to group C and group D. All participants in this study were selected from the Children's Hospital of Chongqing Medical University, Chongqing, China.

Infants who were born full term and without any chronic infectious diseases and infants with an unconfirmed but suspected syndromal diagnosis (as established by the clinical geneticist) were included. Infants with a syndromal or chromosomal disorder with a known influence on physical growth were excluded from the growth and development evaluation.

Methods

Data on diagnosis, sex, age, comorbidities, height, weight and Hb level were extracted from electronic medical records. A 24-h dietary recall questionnaire was conducted for all infants. The questionnaires were performed on the day of admission in group A and group B. On that day, the quantities of food eaten by the infants as measured with utensils used at home (bowl, spoon, cup, etc.) were recorded in detail. Intakes were then calculated using the energy, protein, iron and calcium contents of ingredients outlined in food composition tables (China Food Composition 2016).

Experiments involving human samples were approved by the Institutional Review Board of Children's Hospital of Chongqing Medical University (reference number 2015-68) and conducted in accordance with the principles expressed in the Declaration of Chongqing Medical University.

Hb was measured for the first time after admission. Hb levels were determined by the cyanmethemoglobin determination method. According to the diagnostic criteria of anemia for infants formulated by the World Health Organization (WHO) in 2001, infants aged 6-59 months with Hb levels <110 g/L were diagnosed with anemia.

Anthropometric measurements of the infants were performed after admission using the same electronic baby scale (RCS-20). All measurements were performed in duplicate. Weight was recorded to the nearest 0.01 kg with the infants minimally clothed with bare feet. Height was marked to the nearest 0.01 cm. Anthropometric data were assessed as z-scores for height-for-age (HAZ), weight-for-age (WAZ) and body mass index (BAZ) using WHO Anthro 2005 (http://www.who.int/childgrowth/software/en/) and U.S. National Center for Health Statistics 2006 data. Cutoff points of <-2 standard deviations (SDs) were used to define a low WAZ (underweight), low HAZ (stunting) and low BAZ (wasting); 2≤BAZ≤3 was used to define overweight, and a BAZ >3 was used to define obesity.

Statistical analysis

Data were analyzed by SAS 8.1. The significance level was set at 5%. The Shapiro-Wilk test was used to investigate whether the concentrations of Hb and the anthropometric indicators were normally distributed prior to analysis. Data are presented as means, SDs and medians, as well as 95% confidence intervals (CIs). Variables were compared between control and normal infants in the same age group; the independent samples t-test was used for normally distributed data, and the Wilcoxon signed-rank test was used for nonnormally distributed data. Differences in prevalence were tested with the chi-square test.

RESULTS

Demographics

In this retrospective study, among the infants with ARM, 47 met the eligibility criteria; 44 were boys, and 3 were girls. Twenty-six patients had comorbid cardiac malformations, 4 had urologic comorbidities, 7 had both types of comorbidities, and only 10 patients had no comorbidity. Thirty-six percent of the patients came from urban areas, while 64% came from rural areas. Infants with ARM who underwent colostomy were aged 1.91±1.04 days, had a length of hospital stay of 9.28±3.28 days, had a weight of 3.04±0.58 kg, and had a height of 49.1±2.38 cm. Height and weight in the ARM subgroup who underwent colostomy were not different from those in normal full-term group (data not shown). Among the normal group, 50 infants in groups C and D were randomly selected from the Department of Child Health Care. The age, weight, and height in group C and group D were 6.50±0.60 months and 11.3±0.84 months, 8.12±1.22 kg and 9.81±1.18 kg, and 67.7±2.86 cm and 75.4±3.05 cm, respectively. There was no difference in age between group A and group C. Moreover, there was no significant difference in age between group B and group D (Table 1).

Physical growth and z-score distributions

The anthropometric indices and the z-scores are shown in Table 1. The infants in group A were compared with the normal infants in group C; there was no difference in age between group A and group C, but the HAZ was lower in group A than in group C, while the rates of stunting and overweight were higher in group A than in group C (p=0.003, p=0.02, and p=0.03, respectively). Furthermore, the infants in group B were compared with those who were the same age in group D; the weight, height, HAZ and WAZ were lower in group B than in group D. In addition, the incidence of stunting in group B was significantly higher than that in group D. The WAZ and

Table 1. Physical growth and Z-score distributions

Group	N	Age (months)	Weight (kg)	Length (cm)	HAZ	WAZ	BAZ	Underweight	Stunting	Wasting	Overweight	Obesity
Group A (n=47)	47	7.15±2.26	8.46±1.40	67.3±3.46	-0.84±0.98	0.15±1.48	0.84±1.83	6.4%	14.9%	8.5%	21.3%	2.1%
Group B (n=47)	47	11.6±2.76	9.32±1.04	73.0±3.32	-0.84±0.90	-0.18±1.07	0.39±1.49	2.1%	12.8%	6.4%	6.4%	2.1%
A†	47	5.23±2.63	5.42±1.30	19.6±4.76	0.31±1.80	0.84±1.46	1.29±1.99	6.8%	6.4%	18.1%	-21.3%	-2.1%
p†	-	-	<0.001	<0.001	0.29	0.0003	0.0002	0.29	0.42	0.02	0.0008	0.5
AB†	47	4.44±1.53	0.86±1.10	5.90±4.31	0.20±1.63	-0.34±1.08	-0.81±1.64	4.3%	2.1%	2.1%	14.9%	0
p‡	-	-	<0.001	<0.001	0.51	0.04	0.01	0.61	0.76	0.28	0.04	1
Group C (n=50)	50	6.50±0.60	8.12±1.22	67.7±2.86	-0.12±1.07	0.09±1.30	0.20±1.77	6%	2%	12%	6%	4%
Group D (n=50)	50	11.3±0.84	9.81±1.18	75.4±3.05	0.004±1.19	0.31±0.99	0.43±1.41	4%	2%	4%	10%	2%
p§	-	0.25	0.23	0.6	0.003	0.82	0.05	0.94	0.02	0.57	0.03	0.59
p¶	-	0.21	0.02	0.0002	0.0003	0.01	0.50	0.59	0.04	0.60	0.52	0.96

†*p*: group A compared with the infants who underwent colostomy operations. ‡*p*: group A compared with group B. §*p*: group A compared with group C. ¶*p*: group B compared with group D.

Table 2. Hb parameters and anemia status

Group	Hb (g/L)	Anemia (%)
Group A (n=47)	111±13	36.2%
Group B (n=47)	112±14	44.7%
Group C (n=50)	120±7	4%
Group D (n=50)	120±10	8%
‡*p*	0.55	0.40
§*p*	0.0006	0.0001
¶*p*	0.006	0.0001

‡*p*: group A compared with group B. §*p*: group A compared with group C. ¶*p*: group B compared with group D.

Table 3. Daily consumption of major nutrients in the four groups

	Energy (Kcal)	Energy (% Chinese RNI)	Protein (g)	Protein (% Chinese RNI)	Iron (mg)	Iron (% Chinese RNI)	Calcium (mg)	Calcium (% Chinese AI)
Group A (n=47)	663 (630-701)	88%-97%	17.1 (15.5-18.5)	78%-93%	6.9 (6.6-7.3)	66%-73%	605 (575-640)	230%-256%
Group C (n=50)	723 (710-752)	99%-104%	21.4 (20.1-24.3)	101%-122%	9 (8.9-9.3)	89%-93%	587 (576-610)	230%-244%
p	<0.0001	-	<0.0001	-	<0.0001	-	0.07	-
Group B (n=47)	810 (785-851)	98%-106%	25.7 (23.9-26.7)	96%-107%	8.5 (8.2-8.9)	82%-89%	658 (637-691)	106%-115%
Group D (n=50)	809 (789-881)	101%-110%	26.4 (25.8-27.8)	103%-111%	12 (11.9-12.6)	119%-126%	410 (400-447)	67%-75%
p	0.37	-	0.001	-	<0.0001	-	<0.0001	-

RNI: recommended nutrient intake; AI: adequate intake.
Values are medians (range in 25th and 75th quartiles), with $p<0.05$ (Kruskal-Wallis test).

BAZ as well as the incidence of overweight were lower in the infants who underwent colostomy than those in group A who underwent anoplasty, and the incidence of wasting in the infants who underwent colostomy was significantly higher than that in group A. Moreover, the WAZ and BAZ in group B were significantly lower than those in group A, while the rate of overweight in group A were significantly higher than that in group B.

Hb concentration and anemia

As shown in Table 2, the Hb concentration was significantly lower in the ARM group (group A and group B) than in the normal group (group C and group D), while the incidence of anemia in the ARM group (group A and group B) was significantly higher than that in the normal group (group C and group D). Within the ARM group, there were no significant differences in the incidence of anemia and Hb concentration between group A and group B, and the same result was observed in the normal group.

Diet

As shown in Table 3, group A consumed significantly less energy, protein and iron than group C ($p<0.05$), and the dietary iron intake was only approximately 66-73% of the Chinese recommended daily amount (RDA). Compared to those in group B, the intake of protein and iron was significantly higher in group D ($p<0.05$). The dietary intake of iron was approximately 82-89% of the Chinese RDA in group B.

Nutritional status of infants with additional major comorbidities (including those of cardiac and urogenital origins)

Among the ARM group, 70.3% (33/47) of infants had cardiac malformations, while 23.4% (11/47) suffered from urogenital comorbidities (Table 4). Compared to infants with urogenital comorbidities, those with CHD seemed to be more prone to growth problems and anemia. The BAZ for ARM patients with no comorbidities who underwent anoplasty was higher than that in other patients (median BAZ 2.54, p=0.0016). The BAZ in infants with comorbidities of urogenital origin was lower than that in other infants (median BAZ -1.12, -0.55, -0.34). Infants who suffered from both urogenital and CHD were not found to have lower Z-score distributions than their counterparts (Table 5).

DISCUSSION

It has been reported that children with ARM who require an enterostomy tube suffer from growth problems due to associated congenital anomalies, recurrent hospitalizations, multiple operations and persistent gastrointestinal issues, such as lack of appetite due to abdominal pain and nausea, constipation, diarrhea, and colitis.[12,13] Patients with growth disorders have a higher rate and a longer duration of fistula.[1] Another study has confirmed that most patients who underwent colostomy were not undernourished.6 However, data on the duration of ostomy in those children were not provided.

The patients who were included in the present study maintained fistula status for nearly 1 year. Accordingly, the reported research focused on the impact of 12-month fistula status on growth and anemia in infants with ARM.

We found that infants with ARM who underwent colostomy not only had growth disorders but were also generally obese or overweight. Compared to normative populations with the same age, the HAZ and incidence of stunting and overweight were lower in patients who underwent anoplasty (at nearly 6 months or older). In infants who maintained fistula status for 1 year, the weight, height, HAZ and WAZ at 12 months were lower than the baseline values, and the incidence of stunting did not improve ($p<0.05$). It was shown that the long-term impacts of fistula status on infant length (or height) occurred earlier than those associated with other physical indicators. Nutrients are digested and absorbed mainly in the small intestine instead of the colon. Theoretically, there is little effect on nutritional status in patients who undergo colostomy. The possible reasons for poor nutritional status may be multiple surgical interventions and poor dietary intake in early life. Regarding our preliminary questionnaire completed by the guardians of infants with ARM, we found that most did not know how to feed their infants properly, including the amount, type and frequency of food. The infants were therefore prone to growth disorders or overweight (obesity) due to underfeeding or overfeeding.

Some studies showed that growth failure was not related to the type of malformation (mild or severe), but was related to the presence of a comorbidity.[1] A total of 35% of children had growth problems, and all the growth parameters were below the normal values at all ages ($p<0.01$). In this study, 70.3% (33/47) of the infants with ARM had cardiac malformations, while 23.4% (11/47) suffered urogenital comorbidities. We found that infants with ARM who had cardiac malformations were more likely to exhibit growth disorders (n=33, 70.2%) and anemia (40.4%) than those with urogenital comorbidities. The results of this study were consistent with those of some reports that also found that patients with ARM had more associated congenital anomalies (67%);[14] the most common were cardiac (43.6%) and urogenital (28%) anomalies, and the BAZ was lower than that in healthy infants.

CHD has been recognized as a risk factor for impaired growth and failure to thrive in pediatric patients.[15] Malnutrition is common among children with CHD due to underfeeding and insufficient caloric intake.[16,17] Previous studies have shown that although birth weight for gestational age is usually normal in patients with CHD, young children often present with poor growth parameters. Benjamin J found that children under 2 years old with CHD had high prevalence rates of acute malnutrition (51%) and chronic malnutrition (40%).[18] With the progression of CHD, malnutrition deteriorates due to peripheral hypoperfusion with acidosis and tissue hypoxia, recurrent pneumonia, and pulmonary hypertension.[19] Moreover, some reports noted that growth disorder may occur in patients with urological morbidities.[20] Several mechanisms are involved in the pathogenesis of malnutrition due to renal insufficiency, including lack of appetite, a blunted growth hormone response, metabolic bone disease, perturbed calcium homeostasis and increased catabolism,[21,22] particularly in patients with ARM, who often have urogenital comorbidities.

Table 4. Nutritional status of infants with cardiac and/or urogenital comorbidities

Comorbidity	Operation	Underweight	Stunting	Wasting	Overweight	Obesity	Anemia
Cardiac	Colostomy	5	8	3	0	0	-
(n=26)	Anoplasty	1	2	0	2	1	11
	Fistula closure	0	4	2	2	0	11
Urogenital	Colostomy	0	0	2	0	0	-
(n=4)	Anoplasty	0	0	0	0	0	1
	Fistula closure	0	0	0	0	0	2
Both	Colostomy	1	0	2	0	0	-
(n=7)	Anoplasty	2	0	0	0	0	4
	Fistula closure	0	1	1	0	0	4

Table 5. BAZ distributions in infants with cardiac and/or urogenital comorbidities

Comorbidity	Operation	Mean	SD	95% CI of mean estimate	Lower quartile	Median	Upper quartile	*p* value
Cardiac	Colostomy	-0.37	1.35	-0.93 to 1.84	-0.96	-0.24	0.24	0.21
(n=26)	Anoplasty	0.33	1.62	-0.37 to 1.03	-0.33	0.28	0.68	
	Fistula closure	-0.14	1.65	-0.92 to 0.63	-1.04	0.06	0.68	
Urogenital	Colostomy	-1.05	1.75	-3.83 to 1.74	-2.52	-1.12	0.43	0.79
(n=4)	Anoplasty	-0.07	1.39	-2.28 to 2.14	-0.93	-0.55	0.79	
	Fistula closure	-0.12	0.69	-1.83 to 1.59	-0.67	-0.34	0.65	
Both	Colostomy	-1.24	1.48	-2.61 to 0.12	-3.31	-0.5	-0.12	0.06
(n=7)	Anoplasty	0.31	2.31	-2.10 to 2.73	0.4	1.10	1.75	
	Fistula closure[§]	0.64	1.27	-0.69 to 1.97	-0.15	0.60	1.53	
Neither	Colostomy	-0.57	1.56	-1.69 to 0.55	-1.58	-0.70	0.88	0.0016
(n=10)	Anoplasty	2.52	1.08	1.52 to 3.52	1.79	2.54	3.10	
	Fistula closure	0.30	1.27	-1.27 to 1.88	-0.83	0.24	0.88	

Compared with those in normal infants, a lower concentration of Hb and a higher rate of anemia were observed in patients who underwent enterostomy ($p<0.05$). In this study, some factors, such as a reduced intestinal absorption area, resulted from a prolonged fistula status, and multiple surgical interventions possibly led to anemia. In addition, poor dietary intake in early life leads to poor health and anemia, especially in those lacking supplementation with iron-fortified food (animal-based foods, etc.). Milk has a low iron content. However, in our preliminary questionnaire of guardians of infants with ARM, we found that most did not know how to feed their infants properly, including the proper amount, type and frequency of food. Moreover, most of the infants with ARM were mainly fed formula or breast milk. Because of the fear of intestinal digestive problems, the addition of supplementary food was limited; there was a notable lack of consumption of iron-fortified food during the period in which the enterostomy tube was in place, lasting approximately one year. For the normal children, however, caregivers seemed to be more active in adding meat-based foods to their children's diets. Accordingly, patients with ARM should be routinely screened for anemia and treated promptly for treatable causes.

Conclusion

This study showed that infants with ARM were at risk for growth problems (including malnutrition and overweight or obesity) and anemia. The long-term impacts of fistula status on infant length (or height) presented earlier than those associated with other physical indicators. Compared to infants with urogenital comorbidities, patients with CHD seemed to be more prone to growth disorders and anemia. In clinical practice, we will focus on monitoring physical growth, screening for anemia and standardizing nutrition management for the prevention of growth problems.

AUTHOR DISCLOSURES

The authors report no conflicts of interest.

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