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Original Article

Nutrition status and quality of life in patients with total colonic aganglionosis

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Abstract: Objective: Over the past decades, the quality of life (QOL) of patients with total colonic aganglionosis (TCA) has been significantly improved. This study is to evaluate the long-term outcome of TCA patients in our hospital. Materials: We identified eleven patients with TCA treated from 1999 to 2010. Clinical follow-up data was collected by in-person or telephone interviews. Anorectal function and QOL were evaluated by the Kelly scoring system and Quality of Life Scoring Criteria, respectively. Laboratory results were reviewed and compared with non-TCA patients, including patients with rectosigmoidaganglionosis (RS) or non-Hirschsprung's disease who had colon resection. Results: The defecation frequency of 10 patients was 3 to 6 times per day. All children had Kelly's score of 5 or 6 for anorectal function. Nine patients had satisfactory QOL score and the other 2 patients had fair QOL score. The γ-GT levels in TCA patients were significantly lower than that in non-TCA patients. LDL levels in TCA patients were lower than normal range but of no significant difference compared with non-TCA patients. Conclusions: The long-term outcome of TCA patients was satisfactory in terms of anorectal function and QOL. However, the reduced level of γ-GT and LDL requires further investigations as they might be indicators of potential inflammation for patients with TCA.

Keywords: Total colonic aganglionosis, outcome, quality of life, gamma-GT, LDL

Introduction

About 3% to 15% of patients with Hirschsprung's disease (HSCR) have total colonic aganglionosis (TCA) [1]. Using modified surgical methods such as Modified Duhamel method or ascending colon patch method, the mortality rate can be greatly reduced to below 20% [2, 3]. However, there is little change in mortality rate involving small intestine surgery despite all the supportive treatments [3]. Enterocolitis and sepsis resulted from bacterial infection are the major causes of death [2, 3]. Many factors can affect the immune system, such as long-term parenteral nutrition and bacterial translocation [4, 5]; however, the intrinsic factorsthat lead to immune deficiency remained unclear.

Postoperative anorectal functional recovery is of great importance for patients after surgery. It has been reported that only 52.4% of patients achieved complete recovery ofanorectal function, and the rest had complications that are unrelated to the surgery [1]. It was also reported that some patients suffered from stool incontinence and recurrent enterocolitis that required secondary closure of ileostomy, which significantly compromised life quality [6]. Some retrospective studies have already shown in different centers that there is no ideal operative method for the treatment of TCA with respect to postoperative mortality, morbidity and functional outcomes [7, 8]. Future analyses to assess the long-term outcome of TCA patients would be valuable.

In this study, we have retrospectively analyzed 11 patients with TCA who had received radical surgery in Guangzhou Women and Children's hospital from January 1999 to December 2010. In addition, we evaluated the long-term outcome of anorectal function and life quality. Furthermore, we evaluatedthe laboratory results and compared with non-TCA patients who had intestinal resection, in an attempt to identify the causes of low immune response in TCA patients.

Patients and methods

Subjects

We retrospectively reviewed the medical charts of 11 TCA patients who were treated at Guangzhou Women and Children's hospital from January 1999 to December 2010. All patients were male. Ten patients had two-stage pull-through procedure and one patient (9.1%) had primary pull-through procedure. TCA were confirmed by biopsies that examined in the Pathology Department. Patients who received surgical procedures aged from 6 to 17 months (Median ± SD: 9 ± 4.1 months). Patients' weight at the time of surgery was ranging from 5 to 11 kg (Median ± SD: 7.4 ± 2.1 kg). The Boley method (a stapled side-to-side ileocolostomy with the distal ileum and ileocecus) was performed in 3 patients, and the Solve method (ileum pull-through procedure) was performed in 8 patients. Anal dilatation was performed for 12 to 24 months in all patients. For the comparison of clinical examination, 14 patients with rectosigmoidaganglionosis (RS) (age of 0.5 to 12 months) and 6 patients of non-HSCR who had colon resection (age of 0.5 to 3 months) were included. Prior written and informed consent were obtained from every patient's family and the study was approved by the ethics review board of Guangzhou Women and Children's Medical Center.

All patients with TCA surgery were followed up by the Outpatient Department. The outcome measurements included physical examinations and surveys. The follow-up time ranged from 42 to 171 months (Median ± SD: 72 ± 47.5 months).

Physical examinations

The physical examinations included anus observation and rectal examination, in order to evaluate the function of anal sphincter and to exclude the potential anal stenosis.

Surveys

Assessment parameters include postoperative complications, defecation frequency, stool property, fecal control ability, fecal discernment ability and constipation. Kelly's scoring system was used for anorectal function evaluation including defecation incontinence, soiling and anal sphincter contraction [9]. Among them, defecation incontinence and soiling was assessed by caregivers. Anal sphincter contraction was determined by physicians with the scaling of 2 points for normal, 1 point for fair and 0 point for poor. Quality of life (QOL) questionnaire included caregivers' education, and patients' schooling, diet, social communication and anxiety for diachoresis problems [10].

Laboratory examinations

Fast blood samples of all patients were collected in the morning. Blood count, liver function, kidney function, lipid and trace elements in the blood sample were examined in Clinical Laboratory Department.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software (GraphPad Software, Inc., La Jolla, CA, USA). Data was analyzed using the Student's paired t test or one-way ANOVA for statistical significance. $P < 0.05$ was considered statistically significant.

Results

Clinical outcome

To investigate the long-term efficacy of TCA and to evaluate patients' status of nutrition, a detailed questionnaire was administeredin person or by telephone in the follow-up. All of the 11 patients had postoperative enterocolitis which was diagnosed based on one of the following criteria: (a) defecation frequency increased by 50% and/or present of blood/mucous in the stool; (b) patients showed symptoms of abdominal distention, poor appetite or fever. Three patients received secondary surgery: patient 1 had anastomotic bleeding thus underwent exploratory laparotomy for hemostasis, patient 2 had adhesive ileus surgery three years later, and patient 3 had secondary Seton treatment for anal fistula complications. One patient had recurrent diarrhea and dehydration (every two months) resulted from regular intravenous fluid therapy. Symptoms were improved five years later and the patient has changed to oral rehydration therapy afterwards.

In the follow-up visit, 5 patients (45.5%) had normal anal appearance, 5 patients (45.5%) had mild perianal erosion, and one patient (1%) suffered from perianal neoplasm. None of

Table 1. Demographics and clinical characteristics of 11 Patients with TCA

No.	Age of Surgery (Months)	Follow-up period (Months)	Procedures (Method)	Perianal check	Defecation Control	Defecation Frequency (time/day)	Stool	Kelly Score	Quality of life
1	5	48	Soave	Mild Ulcer	Normal	3-5	Watery	5	10
2	8	84	Soave	Mild Ulcer	Occasional Soiling	>6	Mushy	5	10
3	15	42	Soave	Normal	Occasional Soiling	3-5	Mushy	5	11
4	12	18	Soave	Normal	Normal	>6	Mushy/Normal	6	10
5	6	114	Boley	Normal	Occasional Soiling	3-5	Mushy	5	10
6	12	18	Soave	Normal	Normal	3-5	Mushy	6	9
7	6	113	Boley	Mild Ulcer	Normal	3-5	Mushy	5	9
8	9	47	Soave	Normal	Normal	>6	Mushy/Watery	6	10
9	12	8	Boley	Ulcer	Occasional Soiling	3-5	Mushy	5	8
10	7	96	Soave	Ulcer	Normal	3-5	Mushy	3	7
11	17	147	Soave	Neoplasm	Normal	2-3	Mushy/Watery	5	10

Table 2. Laboratory examinations

No.	ALT	AST	ALP	TP	ALB	GLO	A/G	Cr	TC	TG	HDL	PA	Tf	Urea
1	23	46	ND	65.6	45.4	20.2	2.25	24	3.28	0.88	1.70	238.9	2.97	4.68
2	19	45	ND	70.1	46.8	23.3	2.01	45	3.72	0.38	1.64	180.2	2.47	3.66
3	17	31	178	73.5	43.1	30.4	1.42	33	3.30	2.14	1.19	100.5	ND	2.36
4	15	37	251	65.1	47.1	18.0	2.62	22	3.60	0.69	1.62	265.2	2.93	3.85
5	10	30	ND	59.9	40.6	19.3	2.10	41	3.37	0.57	1.62	233.1	2.00	3.06
6	17	33	177	69.3	45.1	24.2	1.86	21	4.10	0.54	2.18	199.0	2.60	3.11
7	24	31	289	64.5	43.9	20.6	2.13	44	4.22	0.76	2.38	325.1	2.51	3.20
8	14	50	122	85.4	50.9	34.5	1.48	ND	ND	ND	ND	170.6	ND	4.28
9	20	38	170	65.2	44.5	20.7	2.15	23	3.89	1.04	1.20	211.1	2.62	5.32
10	20	35	394	72.8	45.0	27.8	1.62	51	3.05	1.09	1.94	257.1	2.78	7.14
11	10	16	ND	64.8	43.1	21.7	1.99	38	3.43	0.6	1.68	186.5	3.54	2.63
Ref	5-40	5-60	118-390	60-80	35-50	20-29	1.5-2.5	18-62	3.4-5.2	0.23-1.7	0.88-1.8	200-400	2-3.6	2.9-8.9

Abbreviations and units in the table: ALT, alanine aminotransferase, U/L; AST, aspartate aminotransferase, U/L; ALP, alkaline phosphatase, U/L; TP, total protein, g/L; ALB, albumin, g/L; GLO, globulin, g/L; A/G, ratio of albumin to globulin; Cr, creatinine, μM; TC, total cholesterol, mM; TG, triglyceride, mM; HDL, high-density lipoprotein, mM; PA, prealbumin, mg/L; Tf, transferrin; Urea, mM; ND, not-done.

patients had anal stenosis. The sphincter contraction function was satisfactory. No recurrent constipation was identified during the follow-up (**Table 1**). These results indicated that TCAs were of satisfactory anal appearance after corrective surgery.

Assessments of defecation and QOL

To determine the quality of life in TCAs, questionnaire was administered in personor by telephone during follow-up for information of bowel control. One patient (9.1%) defecated 1-2 times per day, 8 patients (73%) defecated 3-5 times per day and 2 patients (18%) defecated more than 6 times per day. Patients had stool of half mushy and half sausage-like (1 case, 9.1%), watery (1 case, 9.1%), mushy (7 cases, 63.6%), and half mushy and half watery (2 cases, 18.2%). Seven patients (63.6%) had normal stool control, and 4 patients (36.4%) had occasional soiling. All patients had good anorectal function in general by Kelly's scoring system, with 5 patients (45.5%) of 5, and the rest (54.5%) of 6. Soiling and food restriction were the two main causes for low QOL in TCA patients. Nine patients (81.8%) had good QOL (9-10 points), while 2 patients (18.2%) had fair QOL scores (7-8 points) (as in **Table 1**). These results indicated that its outcomewas promising.

Laboratory examinations

To evaluate patients' status of nutrition, blood tests were taken. The laboratory results were

Table 3. Laboratory examination

No.	Cu	Zn	Ca	Mg	Fe	K	Na	P	RBC	HGB	HCT	LY	Ly%
1	25.0	62.9	1.62	1.51	8.29	42	88	ND	4.58	129	37.2	6.51	52.4
2	20.6	83.2	1.52	1.43	8.17	44	88	ND	4.79	129	38.2	3.96	42.4
3	21.6	91.9	1.40	1.50	9.53	47	78	1.18	5.23	142	40.9	3.27	43.0
4	24.2	59.0	1.63	1.32	8.04	41	89	1.71	4.73	128	37.2	4.73	65.0
5	29.1	70.8	1.61	1.67	8.63	42	85	ND	4.29	119	35.3	3.21	43.1
6	27.4	79.7	1.65	1.54	7.51	44	89	1.81	5.92	114	36.8	6.50	46.9
7	27.4	85.0	1.51	1.54	8.76	43	81	ND	4.88	130	39.8	2.06	38.8
8	35.4	89.2	1.63	1.93	9.23	47	71	ND	5.21	141	40.9	3.26	45.4
9	31.6	44.7	1.62	1.66	7.77	42	91	2.12	4.48	123	37.1	4.43	40.9
10	22.0	68.1	1.51	1.54	8.96	44	85	1.22	4.82	141	41.2	3.09	34.9
11	22.8	92.4	1.47	1.57	8.41	49	90	ND	5.42	128	39.2	1.94	30.3
Ref	9.3-39.3	76.5-170	1.55-2.10	1.12-2.06	7.52-11.82	30-54	64-108	1.29-1.94	3.79-5.88	110-147	37-51	1-4.80	40-60%

Abbreviations and units in the table: Cu, copper, μM; Zn, Zinc, μM; Ca, calcium, mM; Mg, magnesium, mM; Fe, ferrum, mM; K, potassium, mM; Na, sodium, mM; P, phosphorus, mM; RBC, red blood cell, 10^{12}/L; HGB, hemoglobin, g/L; HCT, hematocrit, %; LY, absolute lymphocyte, 10^{9}/L; Ly%, lymphocyte percentage; ND, not-done.

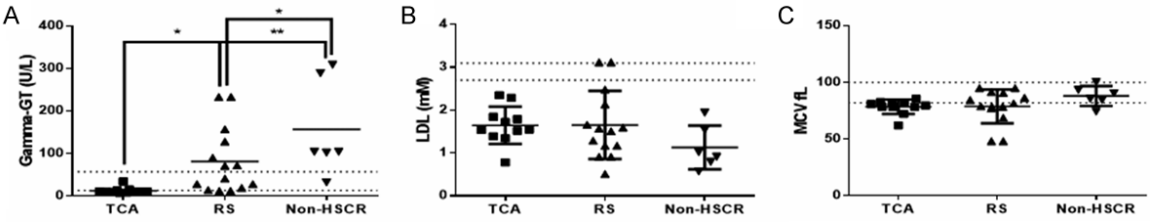

Figure 1. Comparison of γ-GT, LDL and MCV in TCA patients, RS patients and non-HSCR patients who had colon resection. The levels of γ-GT, LDL and MCV were measured and the means were compared. *P<0.05 and **P<0.01. The normal range for γ-GT was 13-57 U/L, LDL of 2.7-3.1 mmol/L and MCV of 82-100 fL, as the dash line in graph.

shown in **Tables 2** and **3**, with normal range of each category listed in last line. Out of the tested 30 parameters, ten were within normal range for all patients, such as AST and ALT. Six parameters were beyond normal range in only one patient, such as ALP and urea. Two patients had abnormal HCT and LY. Four parameters were beyond normal range in 4 patients. Reduced Zn was observed in 5 patients and was nearly 20% below the lower limit of normal range. These results indicated that their nutrition status were satisfying.

Of the 30 parameters, 3 measures showed a reduction in more than 50% of patients. Eight patients had reduced γ-GT levels with an average of 26.0% below the lower limit of normal range, and one patient had a 46.2% reduction. All patients had reduced LDL levels, with an average of 39% lower than the lower limit of normal rang, and one patient had a 71.1% reduction. Six patients had reduced mean corpuscular volume (MCV) levels of 6.4%, and one patient had a 22.3% reduction.

In order to further investigate whether the reduction was associated with TCA, results were compared with non-TCA patients, including RS patients and non-HSCR patients who had colon resection (as in **Figure 1**). There was significant difference in γ-GT level between TCA patients and non-TCA patients (P<0.05 and P< 0.01 respectively). The mean level of γ-GT in TCA patients was 13 ± 7.4 U/L, which is around the lower limit of the normal reference level (13-57 U/L). While RS patients had γ-GT mean level of 84 ± 71 U/L for, and Non-HSCR patients of 157 ± 114 U/L. The mean level of γ-GT in RS and non-HSCR patients were both above the upper limit of normal reference level (**Figure 1A**). There was no significant difference between TCA group, RS group and non-HSCR group for LDL level (1.6 ± 0.44, 1.7 ± 0.80 and 1.1 ± 0.51 mM, respectively). The serum LDL levels of all groups were lower than normal range (2.7-3.1 mM) (**Figure 1B**). Similarly, there was no significant difference between TCA group, RS group and non-HSCR group for MCV level, and the mean MCV level of all three

groups were within normal reference range (80-97 fL) (**Figure 1C**).

Discussion

TCA is a special type of congenital megacolon disease with considerably high mortality rate in the past century [3]. In a 30 years' study in Japan, Satoshi *et al.* reported that the overall mortality of TCA has been reduced from 40.9% to 15.8% and potential enterocolitis reduced subsequently due to modified surgical procedures [3]. In our cohort, all patients survived with only three underwent secondary surgery due to complications. The zero mortality was highly associated with perioperative management. The relatively small patient number may limit generalization of the study results. Prolonged follow-up time and increased sample size are needed in the future.

Postoperative recovery of anorectal function was the major concern in the long-term follow-up. In a 2 to 21 year follow-up study, Menezes *et al.* reported that 47.6% of TCA patients had soiling without correlation with surgical methods [1]. Some of the patients required secondary ileostomies due to severe fecal incontinence and recurrent enteritis that severely negatively impacted the QOL [11]. In our group of 11 TCA patients, 54.5% had a relatively normal anal appearance. Perianal erosion was found in the rest patients, which might be associated with an increased fecal frequency. None of the patients had anal stenosis. The anal sphincter function was nearly normal, with 63.6% patients of normal stool control and 36.4% of occasional soiling. This ratio was roughly equivalent to reports from other centers [1, 12].

Boley and Martin methods have been used for more than decades. Theoretically, this method retains part of the colon for absorption of water, electrolytes and nutrients. However, non-aganglionic colon retention would increase the risk of constipation, enteritis, and anastomotic leakage [13]. Additionally, the surgical methods are time consuming that may increase the risk of postoperative complications. In recent years, the Soave method has been widely used for the reduced anastomotic leakage, necrotizing enterocolitis and hospital stay [13, 14]. This method retains 0.5-1.0 cm of the sphincter and muscular sheath of the rectum, thus it would leave minimal anorectal dysfunction [14]. In our study, 8 patients had Soave method, with all patients of satisfactory Kelly scores and no secondary surgery for recurrent enterocolitis. However, most of the patients had watery or mushy stool due to reduced water absorption. Only one patient had sausage-like stools even 10 years after the surgery. Likewise, 7 cases had an average of 3 to 5 stools per day and three patients had bowel movement frequency of more than 6 times per day. These results were equivalent as in literature reports [1, 7]. The benefit of Soave method was normal anorectal function (100%), relatively reduced soiling (36.4%) [1], and subsequently better QOL in TCA patients (81.8%), compared with RS patients after Swenson method (40%) [6].

In addition to the clinical examinations, patients had laboratory examinations as well. It was found that most of the results were satisfactory. Out of 30 parameters, 19 of them were mostly within the normal range, with exception of 2 patients with high LY level, 1 patient of high TG level, and 1 patient of low Ca level. All of the other abnormal laboratory results were below 20% difference of normal range, even in the parameters that is abnormal in 3-5 patients. Most of the results were satisfactory due to lack of inflammatory diseases during follow-ups.

However, γ-GT, LDL and MCV levels were abnormal in more that 50% patients. The γ-GT level was significantly different between TCA patients and non-TCA patients who had colon resection. γ-GT is an indicator of liver function that can also be detected in intestine [15] and increased γ-GT is commonly found in liver damage, for example, biliary atresia. However, the reason for reduced γ-GT in this study is not clear, given that liver function indicators AST and ALT were in normal range. Considering that non-TCA patients were not followed up long enough, the lowered γ-GT in non-TCA patients needs further investigations with matched time and age groups. LDL reduction was found in all groups, which may result from limited nutrients supply with reduced meat consumption after colon resection in all patients. A recent study showed that gallbladder was one of the organs for cholesterol uptake [16], suggesting that colon resection may directly alter LDL level. It is already shown that LDL is a risk factor for many diseases such as atherosclerosis, however, together with Apolipoprotein B, LDL can preve-

nt bacterial infections such as *Staphylococcus aureus* [17]. In animal models, 50% reduced LDL by 4-aminopyrazolo-(3,4-D) pyrimide would lead to increased morbidity, weight loss and bacterial infection [17]. *Staphylococcus aureus* is shown to be associated with postoperative infection [18]. In our case, all patients had postoperative enterocolitis might be related to low LDL level. Further investigations of larger sample size and nutritional supplementary interventions are needed. MCV is reduced in 6 patients, that is likely resulted from altered blood cell development as the mean Zn level (75.5 μM) was below the lower limit of normal range (76.5-110 μM) and 5 patients had Zn level below the lower limit. The low Zn level is likely due to intolerance and low intake of seafood.

In summary, the long-term follow-up for TCA patients was satisfactory in our study with none recurrence. All patients had good anorectal scores, and most patients had normal defecation control with good QOL scores. The abnormal γ-GT, LDL and MCV levels may due to altered nutritional status and potential bacterial infection risk. Further investigation is needed with larger sample size, matched age and postoperative time in multicenters.

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Disclosure of conflict of interest

None.

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