

# New Perspective for the Management of Near-Total or Total Intestinal Aganglionosis in Infants

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**Background Purpose:** Extensive intestinal aganglionosis is rare. The diagnosis and treatment are known to be difficult and it had been considered to be fatal. The aim of this study was to review our experience with children with extensive intestinal aganglionosis.

**Methods:** Retrospective analysis was conducted in patients referred to the intestinal transplantation unit since 1993. Presentation and outcome were analysed looking at 2 groups who had either undergone previous subtotal intestinal resection (group I) or no or limited resection (group II).

**Results.** Eight children were selected (3 patients in group I and 5 in group II). Group I was remarkable in that patients all were referred early in age with progressing liver failure. Parents of one patient refused to accept transplantation as treatment, and he died one month later. Two noncirrhotic

patients were maintained in the parenteral nutrition programme and currently progress well with enteral feedings. The other 5 patients underwent transplant, and 4 of 5 are alive after transplantation with a mean follow-up of 22.2 months (range 0.4 to 63.6).

**Conclusions:** Subtotal resection of intestine at the time of diagnosis must be avoided. Conservative management with parenteral nutrition may be associated with long-term good outcome. Small bowel transplant may open new perspective in the management of patients with end-stage liver disease. *J Pediatr Surg* 38:25-28. Copyright 2003, Elsevier Science (USA). All rights reserved.

**INDEX WORDS:** Hirschsprung disease, total intestinal aganglionosis, intestine surgical resection, parenteral nutrition, surgical techniques, intestinal transplantation.

**T**OTAL OR NEAR-TOTAL intestinal aganglionosis (NTAG; absence of ganglionic innervation throughout the entire or nearly entire gastrointestinal tract) represents the most extreme and rare form of Hirschsprung's disease.<sup>1-3</sup> It is rare, affecting less than 5% of infants with Hirschsprung's disease.<sup>4</sup> The diagnosis and treatment is known to be difficult,<sup>1</sup> and some consider it to be a fatal condition in infancy<sup>2,3,5</sup> because chronic intestinal obstruction and dependence to long-term total parenteral nutrition (TPN) are associated with high morbidity and mortality rates.

Various palliative treatments have been proposed,<sup>6-8</sup> and recently intestinal transplantation has been undertaken.<sup>9</sup> However, no report has addressed the issues related to modern management, in particular the role of preemptive enterectomy of aganglionic bowel remains controversial. Therefore, we reviewed our experience of NTAG including that of intestinal transplantation in selected cases.

## MATERIALS AND METHODS

All patients referred to the Birmingham Children's Hospital's liver and small bowel transplantation unit since 1993 were reviewed retrospectively. Patients with extensive aganglionosis (extending up to jejunum or above) were selected for the study. The following parameters were recorded: length of aganglionosis, associated malformations, family history of Hirschsprung's disease, condition at referral (age, weight, Z score, serum Bilirubin, platelet count, liver histology),

management methods, types of grafts used in transplanted patients, and outcome.

Patients were divided into 2 groups with group I comprising patients with the whole of aganglionated intestine previously resected, and group II with no (or limited) resection of the aganglionated intestine. Group I and II patients and their outcome was compared.

## RESULTS

Of 110 patients referred between 1993 and 2002, 8 had NTAG (7 boys and 1 girl) with median age of 5.6 months (range, 0.9 to 20.8 months). Patient characteristics are detailed in Table 1. The aganglionosis extended to the proximal jejunum in all patients, with a median length of normal innervated intestine (measured from duodeno-jejunal flexure) of 32.5 cm (range, 10 to 50 cm). Four patients were noted to have associated anomalies—single kidney (n = 3) or hypothyroidism (n = 2). Family history of Hirschsprung's disease was present in 4 pa-

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**Table 1. Patients' Characteristics With Associated Anomalies and Family History**

Case No.	Age at Referral (mo)	Sex	Length of Residual Normal Intestine Distal to DJ Flexure (cm)	Associated Anomalies	Family History	Outcome
<b>Group I</b>						
1	9	Girl	35	Absent left kidney	Nil	Alive
2	2	Boy	30	Nil	Brother + father family history	Alive
3	3	Boy	10	Hypothyroid + absent left kidney	Nil	Alive
<b>Group II</b>						
4	2	Boy	10	Warrdenburg-Shah syndrome	Two siblings	Died
5	12	Boy	35	Absent right kidney	Nil	Alive
6	8	Boy	50	Hypothyroidism	Father and uncle	Died
7	21	Boy	40	Nil	Nil	Alive
8	1	Boy	30	Nil	Nil	Alive

Abbreviation: DJ, duodeno-jejunal.

tients (father or sibling in 2 cases each with one having extensive aganglionosis and Wardenburg syndrome and 3 others having rectosigmoid disease only).

Group I (patients who had preemptive resection of all of aganglionic intestine) consisted of 3 patients (one girl and 2 boys) and group II of 5 patients (all boys). Compared with group II (Table 2), group I was remarkable in that patients were all referred early in age with established cirrhosis, portal hypertension, and progressing liver failure.

Table 3 details management and outcome in these 8 cases. Six patients were listed for transplantation (5 for liver and small bowel transplantation because of associated end-stage liver disease, and one for isolated small intestine owing to thrombosis of superior vena cava), 3 in each group. Patients in group I had to be listed for transplantation much earlier than group II cases as expected from their early presentation with established severe liver disease. Accordingly, they were younger and smaller in size at transplant compared with group II patients. More importantly, because of previous resection of their entire intestine, Group I patients presented with greatly reduced space in the abdominal cavity, which was a major technical challenge for transplanting abdominal organs. Expansion of the abdomen cavity was done in one patient before transplantation by insertion of a tissue expander in the abdomen followed by progres-

sive expansion, which facilitated organ implantation later. A similar operation could not be considered for the 2 other cases in group I, because of their extremely poor condition and severe coagulopathy, and organs had to be reduced in size more than usual for successful transplantation. Patients of group II underwent transplant without specific technical problems.

The parents of one patient declined transplantation as treatment, and the patient died one month later. All 5 other patients underwent transplant (4 liver and small bowel and one isolated small intestine) with a median waiting time of 10.2 months (range, 1.2 to 38 months). One of the 5 patients who received transplants died 7 days after transplantation of graft failure and sepsis. Currently, 4 patients are alive and well after transplantation, with a mean follow-up of 32.1 months (range, 4.4 to 63.6 months). The 2 last patients, who were referred before liver disease was established, were treated successfully conservatively and currently are doing well with continuing home parenteral nutrition and progressing with some enteral feeding.

## DISCUSSION

Hirschsprung's disease involving the entire colon is seen in only 5% of Hirschsprung's patients,<sup>1-4</sup> and NTAG is even less common as reflected in our series

**Table 2. Comparison Between Children Referred With Previous Resection of the Whole Aganglionated Intestine (Group I) and Children With No or Limited Bowel Resection (Group II)**

Referral Parameters	Group I (n = 3)	Group II (n = 5)
Median age at referral (range)	2.9 (1.8-9.5) mo	8.3 (0.9-20.8) mo
Median bilirubin level at referral (range)	109 (66-265) $\mu$ mol	40 (11-359) $\mu$ mol
Platelets at referral (median)	57 (52-81) $10^3$ mL	203 (33-528) $10^3$ mL
Level of aganglionosis (measured from DJ flexure), mean (range)	26 (10-35) cm	33 (10-40) cm
Median age at assessment for transplant (range)	7.4 (5.5-9.9) mo	12.6 (6.6-24) mo
Median weight at transplant (range)	8.1 kg (7.1-9.3)	15.35 kg (9.7-30.7)
Established cirrhosis	3/3	2/4

Abbreviation: DJ, duodeno-jejunal.

**Table 3. Management Type, Types of Grafts, and Follow-Up**

Patient No.	Age at Listing (mo)	Weight at Listing (kg)	Weight at Transplant (kg)	Donor to Recipient Weight Ratio	Type of Graft	Follow-Up (yr)
<b>Group I*</b>						
1	10.2	6.6	8.0	2.7	Reduced liver and small bowel	1.1
2	6.8	7.6	9.0	3.9	Reduced liver and small bowel	3.6
3	7.6	6.0	7.1	2.1	Reduced liver and small bowel	0.4
<b>Group II</b>						
4	8.1	Parents declined transplant				Died
5	17.6	9.8	18	1	Isolated small bowel	5.3
6	11.6	9.7	9.7	6.2	Reduced liver and small bowel	Died
7	Managed conservatively with enteral and parenteral feeding					0.7
8	Managed conservatively with parenteral nutrition					5.0

\*All patients in group I had previous resection of their whole small and large aganglionated intestine. Group II patients had no or limited bowel resection. All patients had stoma at referral.

with only 8 cases referred from the entire United Kingdom in 10 years.

Until 1987 when Ziegler et al<sup>8</sup> reported a first long-term survivor of NTAG, extensive aganglionosis was a fatal condition with a high mortality rate during infancy. This situation has improved in recent years with the advent of total parenteral nutrition and innovative surgical techniques,<sup>3,6,7,10,11</sup> but the very extensive forms of the disease still carrying poor prognosis as reported by Fouquet et al<sup>12</sup> with longer aganglionic segment cases associated with prolonged total parenteral nutrition (TPN) duration and poorer survival rate.<sup>12,13</sup>

In cases of short aganglionic segment, surgical resection of diseased segment and restoration of gut continuity achieve good results and long-term outcome. However, in patients with NTAG, surgical resection does not leave enough normal bowel to support full/enteral feeding, and prolonged parenteral nutrition is necessary. In that context, new surgical options have been considered that retain part of the diseased small bowel, such as right colon patch<sup>4,11</sup> or “myectomy-myotomy.”<sup>8</sup> Results with these techniques still are poor with few reports showing limited success<sup>10</sup> and high rates for postoperative complications.<sup>1,4</sup> Thus overall, most patients with NTAG currently are growing with dependence for TPN and high risk of TPN or disease-related complications in infancy.

In the last decade, intestinal transplantation has emerged as a life-saving procedure for patients with irreversible intestinal failure.<sup>10,14</sup> Severe complications such as progressive liver disease or compromised vascular access accentuate the problems facing these patients.<sup>14,16</sup> Natural history of parenteral nutrition-induced liver failure in small infants often is that of rapid progression and death as suggested by Beath et al<sup>15</sup> who showed that the main risk factor for death within 6 months in children assessed for intestinal transplant was liver disease especially where cholestasis (bilirubin > 100 μmol/L), presence of splenomegaly and cirrhosis on

liver biopsy are present.<sup>15</sup> In this series, of 8 patients, 5 had established cirrhosis at the time of assessment with liver dysfunction and coagulopathy; they thus were proposed for combined liver and bowel transplant. One other noncirrhotic patient received isolated small bowel transplant because he had only one central vein remaining patent. On the contrary, 2 other patients referred early had no cirrhosis and currently are managed by parenteral and enteral nutrition. In both cases, the short segment of normal jejunum allows some enteral feeding which is increased with time as the bowel grows and adapts. Probably they will remain with a stoma for life, but improvement of their condition with age is considered possible.

Three children were referred with previous resection of the whole aganglionated intestine. The rationale for doing this is uncertain and, as far as we know, it has not been proposed for managing NTAG, nor shown to improve outcome. On the contrary, it has been associated, in our experience, with earlier complications, evolution toward liver cirrhosis, and the need to consider transplantation in very young and small infants. The previous resection of the whole bowel resulted in a contracted abdomen, the latter could have reduced their chance of getting a graft in time and did increase technical difficulties for the transplant operation. Group I patients were more technically demanding. Although a high risk of death while waiting for a graft is reported in similar cases,<sup>9</sup> no infant in this series died before transplant. They benefited from new techniques (pretransplant abdominal expansion and the use of en-bloc combined reduced-liver and bowel grafts<sup>16</sup>).

We believe there is no advantage to extensive bowel resection at the time of diagnosing NTAG, and this type of procedure should be avoided. We recommend a simple proximal stoma should be created and attention then be given to (1) use the proximal jejunum optimally,

(2) prevention of complications of parenteral nutrition, and (3) protection of central venous access.

Total or near-total aganglionosis is a rare disease. Small bowel transplant has emerged as a possible surgical treatment for this fatal entity, but earlier referral to expert unit should be considered for preserving the option of continuing conservative management and parenteral nutrition.

Resection of the whole of the intestine at the time of diagnosis should be avoided because it seems associated

with rapid deterioration of liver function and need for transplantation early in life; also it makes pretransplant management more difficult and transplantation more technically demanding.

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## Discussion

*A. Aigrain (Paris, France):* Do you think that one of the prognostic factors in all of these patients is that regardless of whether you succeed to have functioning stoma, even if the duodenum and stomach are not innervated. If not, they quickly become cirrhotic and have to be transplanted quickly. If you have a functioning stoma, it is possible to wait, but it would be advised that these patients should be referred to a specialized unit to consider small intestine and colon transplant. I would agree

not to remove the intestine because of the abdominal space problem that you mentioned.

*K. Sharif (response):* This series is from a centre dealing with transplant only. We do not do the initial and neonatal surgery, but I share your idea that if the stoma is working, then it may give you a better chance of delaying transplant because 2 of our patients currently are treated conservatively with 1- and 5-year follow-up, respectively.