

Does Transitional Zone Pull-Through in Hirschsprung's Disease Imply a Poor Prognosis?

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Purpose: Accurate frozen section interpretation of intraoperative biopsies is critical to the success of the Duhamel procedure. Errors during sampling or interpretation may result in an abnormal pull-through. The authors' aim was to determine the incidence and outcome of transitional zone pull-through (TZPT).

Methods: Ninety-six children who underwent a Duhamel procedure between January 1987 and May 2002 were followed up prospectively. The outcome of 18 children with TZPT was compared statistically with that of a cohort of 58 patients with a ganglionic pull-through.

Results: The incidence of TZPT was 18.8%. Concordance rate between frozen and paraffin-section analyses was 88.5%. The incidence of enterocolitis ($P = .003$) and intractable constipation ($P = .02$) was found to be significantly higher in

TZPT. There was no significant difference in continence ($P = .34$), rectal sensation ($P = .35$), and control ($P = .53$). Five (27.8%) TZPT patients required a revisional surgery for failure of conservative management. The incidence of stoma placement and revision was significantly less in the ganglionic group (3.4%, $P = .007$).

Conclusions: Up to one third of patients with TZPT will require revisional surgery for intractable symptoms. Vigilance is warranted in view of the greater risk of enterocolitis. Continence is not significantly affected.

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ACCURATE INTERPRETATION of intraoperative seromuscular biopsies is critically important to the success of pull-through procedures for patients with Hirschsprung's disease (HD). Errors at sampling or during interpretation may result in the use of transitional-zone colon for pull-through. The long-term outcome and continence of children with transitional zone pull-through (TZPT) is unclear.

The aim of our study was to determine the incidence and long-term outcome of Duhamel TZPT and to compare these results with those obtained from a cohort of patients with a ganglionic pull-through treated at our center over the last 15 years. We review the histologic reasons for this error and suggest means of avoiding this occurrence.

MATERIALS AND METHODS

Ninety-six children with Hirschsprung's disease were treated at St George's Hospital between January 1987 and May 2002. All cases have

been followed up prospectively and clinical data collected on date of birth, age and mode of presentation, age and method of diagnosis, pre-operative management and complications, surgical procedure, early and late complications, and requirement for further surgery. At each follow-up consultation, caregivers were asked to complete a bowel habit questionnaire (Table 1). Clinical and operative records were completed on a total of 76 patients (61 male, male to female ratio, 4.8:1). Children with incomplete prospective details were excluded from the study.

The diagnosis was based on clinical features and abdominal x-rays and confirmed by rectal biopsy. Initial decompression was with warm saline colonic irrigation. Between 1987 and 1994, all patients underwent a staged procedure with initial colostomy or ileostomy formation proximal to the affected segment. From 1995, a proportion of patients underwent a single-stage "primary" Duhamel procedure.

Children were admitted the day before pull-through surgery for bowel preparation with saline irrigation. The surgical technique used was a modification of the Duhamel procedure utilizing a linear stapler.¹ Until May 2002, the extent of disease was established intraoperatively via frozen section analyses of serial seromuscular biopsies and of the "donut" from the distal end of the pulled-through bowel. All tissue was embedded in paraffin and reanalyzed. All 96 pathology reports on diagnostic rectal suction biopsies, intraoperative seromuscular biopsies and "donuts," and all subsequent paraffin section reports were reviewed for this study.

Eighteen cases of TZPT were identified. The continence and outcome results for this group were compared with a cohort of 58 children who underwent a ganglionic pull-through. All clinical data and questionnaire responses were collected prospectively in a Microsoft Excel database. Statistical analysis was performed using the GraphPad Instat Version 3.01. Results were expressed as mean $\pm$ SD. Case-control analyses were analyzed using Fisher's Exact or Mann-Whitney U tests. Statistical significance was assumed when P value was less than .05.

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Table 1. Duhamel Follow-Up Questionnaire

1. Does your child have any of the following-			
a. Incontinence for flatus			
1. No	2. Every month	3. Every week	4. Every day
b. Soiling of underpants			
1. No	2. Every month	3. Every week	4. Every day
c. Incontinence for liquid stool			
1. No	2. Every month	3. Every week	4. Every day
d. Incontinence for solid stool?			
1. No	2. Every month	3. Every week	4. Every day
2. How often does your child go to the toilet?			
1. once a week	2. 1-3 times a week	3. 3/day to 3/week	
4. >3/day			
3. Does she/he know when she/he needs to go to the toilet?			
1. always	2. mostly	3. sometimes	4. never
4. If she/he needs to go to the toilet, is she/he able to wait until it is convenient?			
1. always	2. mostly	3. sometimes	4. never
5. Are there any social problems?			
1. no	2. sometimes	3. often	4. continually
6. What oral medication does your child need?			
1. none	2. laxatives	3. constipators	
7. What rectal medication does your child need?			
1. none	2. small enemas	3. large enemas	
8. Has your child had surgery for constipation or incontinence?			
1. none	2. ACE	3. other	
9. Has your child had any of the following -			
a. Gas bloat/abdominal distension			
b. Vomiting			
c. Diarrhea and fever			
d. Intercurrent infections?			

RESULTS

Eighteen of 96 patients (18.8%) were found to have TZPT. Mean follow-up was 6.0 (± 4.1) years (range, 0.5 to 15). Mean birth weight was 3.24 (± 0.5) kg and age at diagnosis 19.4 (± 37) days. Disease was confined to the rectosigmoid region in 13 cases (72.2%) and extended beyond the sigmoid (long segment) in 5 (27.8%). Trisomy 21 was present in 3 cases (16.7%). At presentation, abdominal distension occurred in 83.3% and bilious aspirates in 94.4%. One preterm infant presented with perforation and peritonitis and required emergency loop ileostomy. Seven children (38.9%) underwent a primary pull-through procedure. The following variables did not differ significantly from those of a cohort of 58 patients with a ganglionic pull-through: birth-weight ($P = .23$), age at diagnosis ($P = .24$), incidence of Trisomy 21 ($P = .44$), or type of procedure ($P = .40$). The extent of disease in the ganglionic group was rectosigmoid in 43

(74.1%), long segment in 10 (17.2%), and total colonic in 5 (8.6%).

All intraoperative frozen-section analyses were reported as ganglionic. Subsequently, paraffin section analyses showed abnormal innervation in 11 cases, giving a concordance rate of 88.5%. In a further 3 cases, analysis of the "donut" showed transitional-zone histology. Aganglionosis was found on repeat biopsy for persisting symptoms in 4 patients whose paraffin sections were ganglionic.

Of the 18 children in the TZPT group, 11 (61.1%) were readmitted with 1 or more episodes of enterocolitis. Of the latter, 1 child was particularly unwell and required a laparotomy, intestinal resection, and stoma formation for necrotizing enterocolitis. He later underwent a repeat pull-through and is awaiting closure of colostomy. Two others with recurrent enterocolitis required an ileostomy. One child underwent revisional surgery and now is well, the other is awaiting a second pull-through. Six children (33.3%) had problems with recurrent abdominal distension and intractable constipation. Three are now treated with a combination of laxatives and enemas, 1 child responded to anorectal myectomy, 1 child has had revisional surgery, and the remaining child has a stoma and is awaiting revision surgery. Overall, 5 children (27.8%) required a stoma for failure of the initial pull-through as a consequence of TZPT. Three children (16.7%) have undergone revisional surgery, whereas 2 are awaiting a second procedure (Table 2).

Twelve families from the TZPT group responded to our continence questionnaire. Three children were lost to follow-up (2 were reported to be well when last seen by our continence nurse) (Table 3). Two patients still had a stoma, and the other was too young for evaluation. Nine patients (75.0%) were fully continent of solid stool, although 2 reported soiling occasionally when stools were loose. Ten (83.3%) were aware of the presence of stool or flatus in the rectum, and 9 (75%) were able to hold on until convenient. Nine children (75.0%) open their bowels between 3 times a day and 3 times a week, 2 do so more often, and 1 less frequently. Two children (16.7%) are incontinent most of the time, and another 2 are incontinent on average once a week.

Of the cohort of patients with a ganglionic pull-through, 13 (22.4%) were readmitted with enterocolitis. This was significantly less than the incidence in the

Table 2. Outcome

Outcome	Transitional Zone Pull-Through (n = 18)	Ganglionic Pull-Through (n = 58)	Significance
Enterocolitis	11 (61.1%)	13 (22.4%)	$P = .003$
Intractable constipation	6 (33.3%)	6 (10.3%)	$P = .002$
Number requiring stoma	5 (27.8%)	2 (3.4%)	$P = .007$
Revisional surgery	3 (27.8%)	2 (3.4%)	$P = .08$

Table 3. Continence

Continence	Transitional Zone Pull-Through	Ganglionic Pull-Through	Significance
Mean (SD) continence to solid stool*	1.8 (1.2)	1.3 (0.8)	$P = .17$
Mean (SD) rectal sensation*	1.8 (1.1)	1.5 (0.9)	$P = .35$
Mean (SD) ability to retain*	1.8 (1.0)	1.5 (1.0)	$P = .53$
Mean (SD) soiling incidence*	1.9 (1.1)	1.4 (0.9)	$P = .10$

*Score range, 1 (normal) to 4 (intractable problems).

TZPT group ($P = .003$, RR 3.4). Intractable constipation was significantly less frequent ($n = 6$, 10.3%, $P = .02$, RR 2.7). Nevertheless, 2 children (3.4%) required a stoma ($P = .007$, RR 3.8) and later revisional surgery. The indications were associated intestinal neuronal dysplasia unresponsive to conservative management in 1 child and inadvertent twisting of the colon at pull-through in another.

The families of 46 patients from the ganglionic group answered our continence questionnaire. Seven children were no longer under review but had normal continence and bowel activity when last seen. Four patients were too young to report on continence, and 1 child had a stoma. Normal continence was reported by 39 children (84.8%). Four children (8.7%) were incontinent on average once a month, and 3 children (6.5%) reported being incontinent most of the time. A total of 82.6% had normal rectal sensation and were able to retain stool until they reached an appropriate place. A normal bowel habit was reported by 42 children (91.3%). Thirty-five (76.1%) children never soiled. Seven (15.2%) soiled occasionally, and 4 (8.7%) soiled most of the time. There was no significant difference in fecal continence ($P = .17$), sensation ($P = .35$), control ($P = .53$), bowel habit ($P = .66$), or soiling ($P = .10$) between the TZPT and ganglionic groups.

DISCUSSION

Histologically, the transition zone in HD is characterized by diminished numbers of ganglion cells in the myenteric plexus and submucosa. Whole-mount preparations also show increased irregularity and wider spacing of the polygonal network of ganglia and nerve fibers of the myenteric plexus. Occasional acetylcholinesterase-staining hypertrophic bundles of extrinsic nerves also are seen.^{2,3} White and Langer⁴ have shown that the circumferential distribution of the transition zone is uneven, with a "leading edge" of ganglion cells in both myenteric plexus and submucosa extending into the aganglionic distal bowel. They also showed that the maximum length of this leading edge was 2.4 cm and 2.1 cm in the myenteric plexus and submucosa, respectively.⁴ Ganglion cells at the tip of the leading edge were present in clusters of up to 6 ganglion cells in marked contrast to an absence of ganglion cells for most of the remainder of the circumference.⁴ The leading edge was

more frequently observed along the antimesenteric border.⁴ It follows that a point biopsy may appear to be ganglionic, or aganglionic, depending on its position on the circumference (Figs 1 & 2). This explains why biopsy specimens taken from the pull-through at a later stage may turn out to be abnormal. Although case reports of zonal colonic hypogangliosis and acquired agangliosis⁵ have been published, the existence of this entity is questionable.

The accuracy of frozen-section analysis depends on the number of levels examined from each biopsy. Morphologically, ganglion cells from very young infants are different from those in adults. They are smaller, have less cytoplasm, and have much smaller nucleoli.⁶ The morphologic immaturity of ganglion cells contributes to the difficulty in frozen-section interpretation in very young children. Ganglion cells normally are more numerous in the myenteric plexus than in the submucosal plexus, making frozen-section evaluation of superficial biopsies especially difficult.⁶ The concordance rate between frozen and permanent-section analysis of intraoperative biopsies at our center was 88.5%. This rate is comparable with that of 89% published in the pathologic literature.⁶ This figure may be improved on if more sections of the

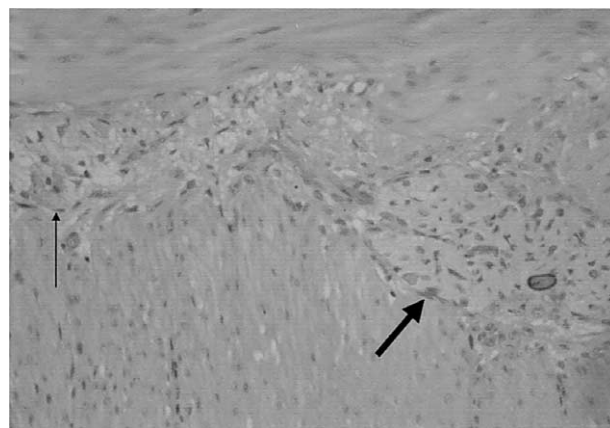


Fig 1. Excised bowel at original Duhamel procedure. Although ganglion cells are present at one point on the circumference (thin arrow), a single large nerve is present nearby within the intermyenteric plexus, (thick arrow), 1.5 mm from the proximal margin (ie, from the primary anastomosis), suggesting focal persistence of transition zone.

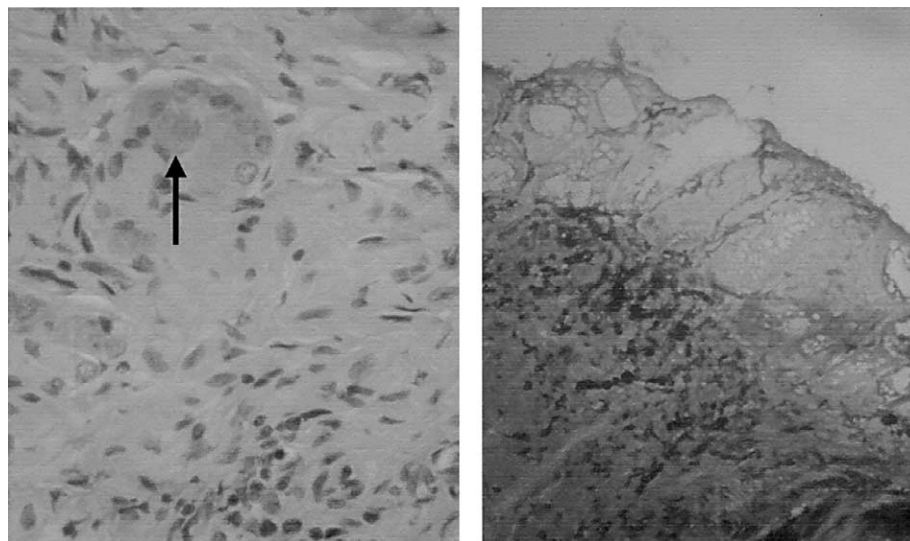


Fig 2. Biopsy of "pull-through" bowel. Ganglion cells are present (H&E stain; arrow on left), but there is an abnormal acetyl-cholinesterase staining pattern (right).

specimen submitted are reviewed. However, it is not practical to section and review the entire specimen while an infant is under general anesthesia.

The outcome of TZPT is covered poorly in the surgical literature. Ghose et al⁷ carried out a retrospective study of 13 children with TZPT. Incidence of TZPT was 14.8%, and their technique did not involve frozen-section analysis. In their experience, no child with a TZPT had normal bowel control, the majority reporting fecal leakage and soiling. Four children (30.8%) suffered intractable constipation, and 6 more (46.1%) had persistent diarrhea and soiling. One child was readmitted with enterocolitis. Seven children (54%) underwent repeat pull-through procedures. Only one of these is continent. Our experience was different in that we found no significant difference in continence between our TZPT and ganglionic groups. Of our TZPT children, 75% were fully continent of solid stool, and 83.3% reported having normal sensation. Normal bowel frequency and ability to retain stool was reported by 75%. Two children (16.7%) were incontinent. Less than one third of this group required revisional surgery.

TZPT after the Duhamel procedure may occur because

of errors in sampling, histologic interpretation, and surgical technique. The majority of children with TZPTs have symptoms, the most common of which are enterocolitis and intractable constipation. Continence, sensation, and bowel frequency did not appear to be significantly different from that of children with a ganglionic pull-through. A number of children will respond to medical treatment, gentle dilatation, or anorectal myectomy. However, up to one third of cases require a stoma before revisional surgery.

We are now using 2 different techniques to minimize these complications. One involves a 2-stage procedure, in which frozen-section analysis is used to identify normal innervation of a segment, which then is brought out as a stoma. The opportunity exists for paraffin section analysis confirmation before using the stoma for pull-through. When a primary Duhamel is carried out, bowel at least 5 cm proximal to the most proximal ganglionic biopsy is utilized for the pull-through to allow for the sampling error incurred if the "leading" ganglionic edge was biopsied. The "donut" submitted for frozen-section analysis is studied circumferentially in a large number of sections before stapling.

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