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Persistence of Abnormal Gastrointestinal Motility After Operation for Hirschsprung's Disease

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OBJECTIVE: Recent studies in patients with Hirschsprung's disease (HD) suggest that morphological abnormalities of the intramural intestinal plexuses are not restricted to the colon. In this report, symptoms and objective tests of gastrointestinal (GI) motor dysfunction were determined long after operative treatment to see whether evidence of a more widespread and relevant motility disturbance could be detected.

METHODS: Twenty-one children were available for study an average of 6.6 yr after surgery for HD. All of these patients underwent evaluation of bowel frequency per week, total GI transit time (TGTT), and a scintigraphic gastric emptying test using solid food; anorectal manometry and segmental colonic transit times were performed in a subset of patients. Results were compared with findings in appropriately matched controls.

RESULTS: Frequency of defecation per week in patients with HD after surgery was not different from that in control children, but TGTT was significantly longer ($p < 0.01$). Percentage retention of gastric isotope at 60 min exceeded the normal range in 12 of 21 (57.1%) patients, and colonic transit was abnormal in all six children studied. Symptoms persisted in two-thirds of patients postoperatively, and transit abnormalities were more common in the symptomatic subset ($p = 0.026$).

CONCLUSIONS: Our data show that, in a subset of patients with HD, GI motor dysfunction persists long after surgical correction. The heterogeny of basic defects responsible for HD could provide the substrate for these motor abnormalities that, in turn, seem at least partially responsible for continuation of the symptomatic state. (Am J Gastroenterol 2000;95:1226–1230. © 2000 by Am. Coll. of Gastroenterology)

INTRODUCTION

Data are accumulating to indicate that Hirschsprung's disease (HD), a disorder once thought to exclusively involve an aganglionic segment of distal colon, also affects motor function in other parts of the gut. The variability in manifestations could reflect the heterogeneity of basic genetic defects now recognized as being responsible for the phenotypic expression of HD (1–3). Recognizable abnormalities in esophageal motility are common, and duodenal motor dysfunction is present in 48% of patients (4, 5). Although recent preliminary data indicate that small intestinal motor dysfunction can be detected after operative treatment for the disease (6), some question remains regarding the contribution of the obstructed colon or perioperative condition toward the measured proximal gut motor abnormalities and symptoms.

We have followed a large cohort of children for at least 2 yr beyond the time of operative treatment for HD. These children participated in a follow-up study to determine the persistence of motor abnormalities throughout the gut; this would further support the concept that HD is a diffuse GI motor disturbance, at least in a subset of patients with the disorder. We also were interested in the relationship of symptoms to presence and type of motor abnormality, information that could be useful to the clinician posed with evaluating symptomatic children with histories of previous treatment for HD.

MATERIALS AND METHODS

The study group consisted of all surviving patients treated surgically for HD at least 2 yr previously by the Division of Pediatric Surgery, Naples, Italy. The study was conducted between December 1994 and December 1996. Forty families were invited by letter or by telephone to participate. Twenty-one children (mean age ± SD, 11.8 ± 4.0 yr; range: 3.4–17.0 yr) were included in the study after the parents gave informed consent for their participation; the parents of 10 patients declined the invitation and nine patients had been lost to follow-up. Of those who participated, the Soave surgical procedure had been performed in eight (38.1%), the Duhamel in nine (42.8%), and an anorectal myectomy in four (19.0%).

Clinical information from the time of the diagnosis was obtained for each patient through review of medical charts. In each patient, HD had been diagnosed by a combination of findings from barium enema, anorectal manometry, and suction or deep rectal biopsies. The preoperative barium

enema revealed a narrowed segment limited to the rectum and rectosigmoid in 13 children (61.9%); in five others (23.8%) this segment extended into the transverse colon. In the remaining three subjects (14.3%), colonic dilation was present to the anus without a conspicuously narrowed segment. In each case, presence of ganglion cells at the proximal level of the surgical resection was confirmed histologically. The rectoanal inhibitory reflex by anorectal manometry was absent in all subjects at the time of diagnosis, and ganglion cells were not found on rectal biopsy specimens.

Follow-up evaluation included symptom assessment and objective measures of GI motor function. A structured questionnaire was used to assess bowel habits, soiling episodes, recurrent fecal impaction, vomiting, diarrhea, abdominal distention, abdominal pain, anorexia, and any use of laxatives. A standard protocol was prospectively applied to evaluate weekly frequency of defecation. Because we were primarily interested in gastric and total gut transit, total GI transit time (TGTT) and scintigraphic gastric emptying of solid food were measured in all subjects using methods described later. Anorectal manometry was repeated in 19 of the 21 patients, and segmental colonic transit times (SCTTs) and rectal suction biopsies were performed in a subset of six children with both abnormal weekly defecation frequency and prolonged TGTT.

For 3 days preceding TGTT, SCTTs, and anorectal manometry, subjects underwent daily enemas to prevent impaction and remained off all laxatives and/or suppositories during the measurements. To determine TGTT, 20 polyethylene radiopaque markers (5-mm diameter) were swallowed at breakfast with milk. The feces from each subsequent bowel movement were collected and examined radiographically; the process was continued until excretion of ≥80% of the markers occurred (7). SCTTs were measured using 20 radiopaque markers of each of three different shapes that were swallowed over 3 consecutive days, respectively; the SCTT for each segment was expressed as mean daily percentage output of markers (transit index) from each colonic segment (8). Retention of contents in a given segment was considered abnormally prolonged if the mean transit index was ≤60%, because the lower confidence limit of a normal adult population was greater than this value (8). Anorectal manometry was performed using a triple-lumen polyethylene catheter and previously reported methods; anal resting pressure, rectosphincteric inhibitory reflex, and rectal compliance were determined (8). Scintigraphic gastric emptying studies were performed with a method reported elsewhere (9). TGTT, anorectal manometry measurements, and gastric emptying results were compared to similarly determined findings in a group of 11 control children who have been reported previously (8). For rectal biopsies, both a search for ganglion cells and histochemical acetylcholinesterase (AchE) staining were performed, following the method of Risdon on suction (Noblet capsule) biopsies (10).

All data are reported as mean ± SD throughout. Mean values across patient groups were compared by using an unpaired, two-tailed Student's *t* test. Group proportions were compared using Fisher's exact and log-likelihood ratio tests, considering the small cell sizes. Pearson's r is reported for correlational statistics. A p value <0.05 was uniformly required for statistical significance.

Table 1. Anorectal Manometry Results in Patients and Control Subjects

Measured Parameter	Hirschsprung's Disease* (n = 19)	Control Children (N = 11)
Maximal anal pressure, mm Hg	122.7 ± 13.6	110.0 ± 15.3
Resting anal pressure, mm Hg	75.9 ± 15.5	68.5 ± 21.3
Anal pull-through pressure, mm Hg	118.0 ± 20.0	102.1 ± 23.6
Rectal compliance, ml/mm Hg	1.6 ± 0.6	1.8 ± 0.7

* After operative treatment.
Data reported as mean ± SD; no difference was statistically significant.

RESULTS

Each subject studied continued to show an absence of rectoanal inhibitory reflex on anorectal manometry. However, maximal and resting anal pressure, anal pull-through pressure, and rectal compliance were not different from those in the control group (Table 1). Rectal suction biopsies showed the presence of ganglion cells but absence of AChE fibers in all six of the biopsied patients.

Although the frequency of defecation per week in the HD patients did not differ from that in the comparison group (4.6 ± 2.8 stools per week [range: 0–10] *vs* 5.3 ± 2.9 stools per week [range: 3–9]; $p > 0.4$), TGTT was significantly longer in the patients with HD after surgery than in 11 age- and gender-matched control children (71.6 ± 29.5 h [range: 22–120] *vs* 29.8 ± 9.4 h [range: 22–39]; $p < 0.01$). In particular, 14 patients (66.6%) had a bowel frequency in the control range, whereas only five (23.8%) had a TGTT in the control range. SCTT demonstrated that some of the abnormality in TGTT was related to residual delay in colonic transit. Delayed transit at the level of the distal segment was found in four of the six studied patients with constipation and at the level of the right colon in the remaining two patients. These findings were unrelated to extent of the preoperative aganglionic segment.

Percentage retention of gastric isotope at both 60 and 90 min was significantly longer in the patients compared with controls (at 60 min: 62.4 ± 9.6% *vs* 43.3 ± 8.7%; at 90 min: 47.9 ± 7.8% *vs* 37.4 ± 3.9%; $p < 0.001$ for each comparison). In 12 of 21 patients (57.1%), percentage retention of gastric isotope at 60 min was >2 SD beyond the mean value for normal children (Fig. 1). Ten (83.3%) of the 12 children with delayed gastric emptying also had a prolonged TGTT, but the two measures were poorly correlated overall (Fig. 2). In one patient whose aganglionic segment extended to the transverse colon, gastric emptying was mildly delayed and the TGTT was normal. In contrast, gastric emptying was

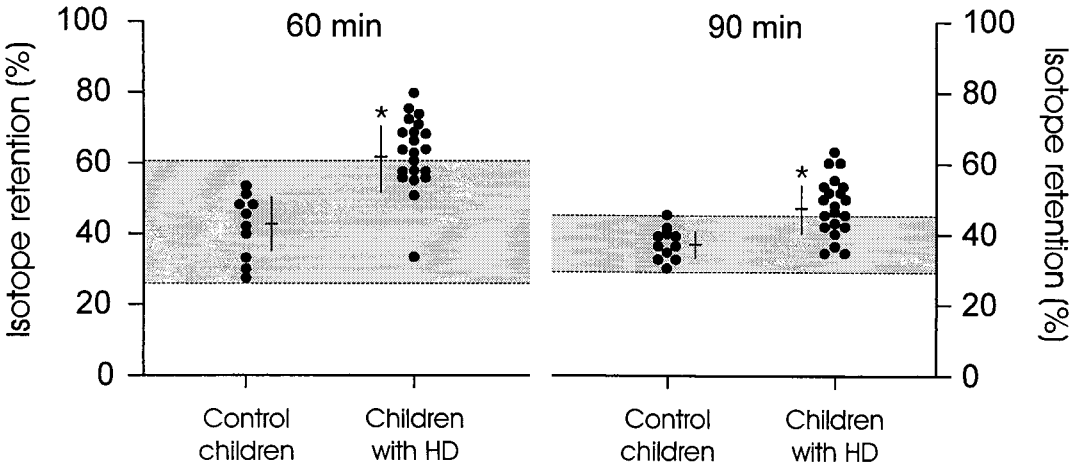

Figure 1. Gastric emptying of solid food in children with Hirschsprung's disease when compared with control subjects. Values are given at 60 and 90 min after the test meal. The shaded area represents 2 SD around the mean of the controls for each time period. Cross-hairs indicate mean ±SD. *$p < 0.001$ compared with controls.

markedly delayed and TGTT was abnormal in two of the three subjects in whom aganglionosis was limited to the anus. Examined in another way, abnormal gastric emptying was found in 40% of patients with both normal bowel frequency per week and normal TGTT, whereas two-thirds of the patients with normal gastric emptying study had an abnormal bowel frequency per week and an abnormal TGTT. There were no measurable differences in subject age, time elapsed since surgery, symptomatic presentation, or time to diagnosis between groups with or without transit abnormalities in this study.

Clinical symptoms at diagnosis and on follow-up are reported in Table 2. Additionally, a history of recurrent fecal impaction was reported by 10 patients (47.6%) before operation that continued postoperatively in three (14.2%). No patient had symptoms before or after surgery to suggest esophageal motor dysfunction. Individual symptoms at the time of follow-up evaluation did not have specific predictive ability for the measured transit abnormalities, but the symptomatic state was more commonly associated with abnormalities of some type ($p = 0.026$; Table 2). Delayed gastric emptying was present in 71% of patients with some residual symptoms, whereas this abnormality was found in less than a third of the asymptomatic group. Likewise, TGTT was more often abnormal in the symptomatic subset, but these differences did not reach statistical significance.

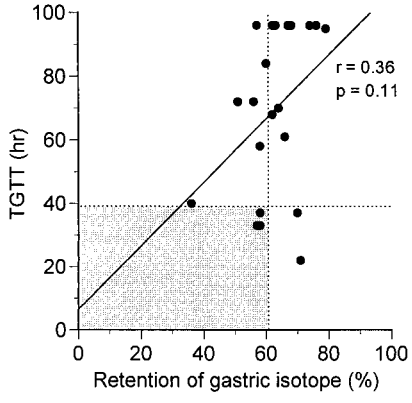

Figure 2. Relationship of total GI transit time (TGTT) to gastric emptying at postoperative evaluation. Thresholds for normal values are shown with dotted lines; the shaded area represent normal values on both studies. Gastric emptying values are given for the 60-min evaluation.

DISCUSSION

This is the first systematic study of various aspects of GI motor function in children with HD long after removal of the aganglionic colonic segment. Previous studies have suggested that motor abnormalities could be found in presumably uninvolved regions, and symptoms in some children with HD seem more widespread than one might expect from colonic dysfunction alone (4–6). However, general health usually improves dramatically after removal of the conspicuously abnormal aganglionic segment, and little attention has been given to extracolonic motility in this disorder. We show in this group of subjects that GI symptoms, including vomiting, distension, and poor growth, persisted in a reasonable subset of patients, observations that support the potential relevance of more extensive gut neuromuscular dysfunction.

Previous studies have shown that esophageal motility abnormalities are more common in HD patients, even when the children are studied shortly after surgical treatment (4). Likewise, abnormalities in duodenal motor activity seem more common in these children shortly after operation (6). Delaying the study of these subjects well away from the operative period, however, may be important to avoid detecting changes attributable to the chronically obstructed

Table 2. Symptoms at Presentation and Follow-Up and Their Relationship to Transit Abnormalities

			In Relation to Children With Symptom at Follow-Up		
Symptom	No. With Symptom at Presentation, n (%)*	No. With Symptom at Follow-Up, n (%)*	Abnormal Gastric Emptying, n (%)†	Abnormal TGTT, n (%)‡	Any Transit Abnormality, n (%)
Vomiting	12 (57)	5 (24)	4 (80)	3 (60)	5 (100)
Abdominal distention	17 (81)	3 (14)	2 (67)	2 (67)	3 (100)
Failure to thrive	7 (33)	2 (10)	1 (50)	2 (100)	2 (100)
Constipation	21 (100)	6 (29)	3 (50)	6 (100)	6 (100)
Incontinence	0	7 (33)	5 (71)	7 (100)	7 (100)
Any symptom	21 (100)	14 (67)	10 (71)§	12 (86)‖	14 (100)¶
No symptom	0	7 (33)	2 (29)	4 (57)	4 (57)

* Percentage of all children, n = 21; † p 0.84 across symptoms; ‡ $p = 0.12$ across symptoms; § $p = 0.16$ compared with asymptomatic children; ‖ $p = 0.28$ compared with asymptomatic children; ¶ $p = 0.026$ compared with asymptomatic children; TGTT = total gastrointestinal transit time.

colon or to nutritional or psychophysiological parameters that could influence gut motor function (11). This investigation involved only children who had undergone surgery at least 2 yr earlier, and little influence of the preoperative or perioperative period would have remained. Despite this, we found that all transit measurements (gastric, colonic, and total gut) were longer in the children with HD as a group than in control children. Delayed transit (gastric or total gut) was not clearly predicted by individual symptoms but was more commonly associated with persistence of the symptomatic state.

The conspicuous colonic manifestations of HD are now recognized as a component of the phenotypic expression of various genetic defects (12). Each interferes with the processes involved in the migration and differentiation of the enteric neurons from the neural crest. Both intracellular proteins and extracellular matrix interactions seem responsible for these steps during embryogenesis (13). Recent data strongly suggest that an interaction of endothelin-B receptor with its physiological ligand EDN-3, as well as of RET receptor with its ligand glial cell line-derived neurotrophic factor, are crucial for the development of specific neural crest-derived cell lineages (1–3). These include melanocytes and sensory, autonomic, and enteric neurons. A genotype-phenotype correlation study will be required to see if different genetic defects are actually responsible for the different clinical manifestations of this disease. Now that motor dysfunction is recognized in some subjects in regions other than the aganglionic segment and that symptoms do not necessarily predict the involved organs, a careful study with objective tests of motor function will be necessary to draw firm conclusions. The recognition may also help explain previous observations of the inconsistent relationship between degree of conspicuous colonic involvement and clinical course (14, 15).

Gastric emptying abnormalities in patients with Hirschsprung's disease have not been reported previously. Delayed emptying may be partially responsible for the anorexia, vomiting, and failure to thrive that is found in a large number of subjects at presentation and that persists in some after surgical treatment. Several other observations in these children deserve comment. Prolonged TGTT in subjects with normal gastric emptying could relate to a delay in small bowel transit (as seen in some adults with chronic constipation) or at the level of the neorectum (16). The fact that some patients with normal bowel habit frequency had prolonged TGTT suggests that frequent bowel movements of small quantity must have confounded the usual correlation between bowel movement frequency and gut transit. Colonic transit studies are normally based on measurements from unoperated colons, relying on normal landmarks (8). Consequently, the levels of delay may have been influenced partially by the altered location of the colon after surgery. Nevertheless, the delays detected in subjects with partial colectomies probably do reflect persistent colonic dysfunction, as the surgical effects, if any, might have been expected to shorten transit time. The rate of incontinence in our patients after surgery was not higher than that reported by others (17). Although the population is heterogeneous from the surgical standpoint, it is unlikely that the type of operation would have influenced our conclusions.

In summary, this study demonstrates persistence of GI motor dysfunction in the majority of children with HD long after surgical treatment of the aganglionic colonic segment. Objective abnormalities include abnormal colonic transit, delayed total gut transit, and previously unrecognized delays in gastric emptying. Persistence of symptoms uniformly indicates presence of measurable transit abnormalities, although individual symptoms may be poor predictors of the location of transit error. Transit abnormalities are also found in more than half of asymptomatic children, suggesting that additional factors are required to induce the symptomatic state. An evolving understanding of the genetic defects responsible for varied manifestations of the disease may help in predicting the extent of GI tract dysfunction in the individual case. In the meantime, the clinician caring for patients with HD should be aware that the disorder and its manifestations are not as localized to an aganglionic colonic segment as once thought and that HD may remain a suitable explanation for postoperative symptoms in some subjects.

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