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Effect of colon transection on spontaneous and meal-induced high-amplitude-propagating contractions in children

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Abstract

Background—After Hirschsprung's disease (HD) surgery, many children suffer fecal incontinence caused by increased number of high amplitude propagating contractions (HAPCs) propagating through the neorectum to the anal verge. The aim of this study was to determine whether children with HD have more HAPCs than children with colon transections for reasons other than HD.

Methods—We reviewed 500 colon manometries. Children (7.6 ± 5.1 yrs; 275 male) with functional constipation ($n=237$; 7.4 ± 5.0 yrs; 126 male) and chronic abdominal pain ($n=48$; 9.8 ± 5.8 yrs; 25 male) served as controls compared to subjects with HD ($n=56$; 6.9 ± 4.1 yrs; 44 male) and colon transection for other reasons ($n=24$; 6.1 ± 5.8 yrs; 12 male). We excluded 139 subjects without HAPCs. We documented HAPCs during 1 h fasting and 1 h postprandial. Results are mean $\pm$ SD.

Results—During fasting, HD subjects had more HAPCs ($2.2 \pm 3.4/h$) vs. functional constipation ($0.8 \pm 2.2/h$, $p=0.0004$) and chronic pain ($0.5 \pm 1.1/h$, $p=0.001$), but not more than colon transection ($1.9 \pm 3.2/h$, $p=1.0$). HD showed more postprandial HAPCs ($4.0 \pm 5.4/h$) than functional constipation ($1.5 \pm 2.5/h$, $p<0.0001$) and chronic pain ($0.9 \pm 1.6/h$, $p<0.0001$), but not more than colon transection ($2.4 \pm 3.0/h$, $p=0.6$). There were more HAPCs fasting and post-prandial after colon transection ($1.9 \pm 3.2/h$ and $2.4 \pm 3.0/h$) than functional constipation ($0.8 \pm 2.2/h$, $p=0.3$ and $1.5 \pm 2.5/h$, $p=1.0$) and chronic pain ($0.5 \pm 1.1/h$, $p=1.0$ and 0.9 ± 1.6 , $p=1.0$). HD subjects were divided by chief complaint:

fecal incontinence or constipation. HD subjects with incontinence (n=23) only had more HAPCs fasting (p=0.01) and post-prandial (p=0.01) than HD subjects with constipation (n=28) only.

Conclusions—Increased HAPCs followed colon transection, regardless of cause. HD subjects with incontinence had more HAPCs than subjects with colon transection for other reasons.

Keywords

Hirschsprung's Disease; High Amplitude Propagating Contractions; Fecal incontinence; Constipation; Colon Manometry

Introduction

Hirschsprung's disease (HD) is characterized by absent of ganglion cells in the distal bowel beginning at the anal sphincter and extending proximally for a variable distance. Surgeons remove the aganglionic segment, and restore continuity¹. Years after surgery, a majority of patients suffer from fecal incontinence². Fecal incontinence after successful surgery appeared to be caused by increased numbers of high amplitude propagating contractions (HAPCs) from healthy colon through the neorectum to the anal verge³⁴⁵⁶. HAPCs are the manometric marker for colon neuromuscular health and are associated with an urge to defecate⁷. In healthy subjects HAPCs usually end in the sigmoid, dumping luminal contents into the rectum, and allowing a choice about defecation or not. In HD, the rectum has been resected, and powerful pressures propagate to the anus, overwhelming attempts to avoid defecation.

Colon manometry provides a record of colon motility. Features of normal colon motility include HAPCs and a gastrocolonic response, the variable increase in motility that accompanies a meal. HAPCs are defined by pressure increases with amplitudes ≥ 60 mmHg that propagate ≥ 30 cm from the proximal to the distal colon⁸. Several factors are involved in the generation and regulation of HAPCs. Extrinsic pathways provide an exchange of information between the CNS and the colon via spinal pathways⁹. Parasympathetic signals travel via the pelvic nerves to the colon and rectum, and sympathetic fibers travel to the colon from sympathetic ganglia, whose primary neuronal cell bodies are located in the lumbar region of the spinal cord. Sympathetic neurons are a source of tonic neural inhibition to the colon; patients with lumbar spinal cord lesions demonstrate colonic hypermotility¹⁰. The sympathetic receptor α_2 is present throughout the colon. When an agonist to this sympathetic receptor was given to healthy individuals, subjects had increased HAPCs¹¹. Spinal stimuli to parasympathetic pelvic nerves stimulate colonic activity⁹. Therefore, interruption of parasympathetic nerves to the colon results in loss of coordinated contractions¹⁰.

Previous studies established that patients with Hirschsprung's Disease have increased frequency of HAPCs after surgery compared to children without surgery³⁴. The mechanism for this increase is unknown. It may be due to loss of intrinsic inhibitory tone and pacemaker dysfunction or loss of extrinsic inhibitory control. Another possibility includes an increase in excitatory forces from either pacemaker dysfunction or extrinsic stimulation. The purpose of this research is to assess if children with HD experienced more HAPCs during colon

manometry than children who had colon transection, and children with normal anatomy. These data may offer a mechanistic explanation for too many HAPCs⁸.

Methods

The Human Subjects Committees at Louisiana State University Health Science Center and Children's Hospital of New Orleans approved this retrospective chart review. We reviewed records of 500 patients who had colon manometry between 1988 and 2013 at four institutions: Harbor-UCLA Medical Center, Children's Hospital of Orange County, CA, University of Kansas Children's Hospital, and Children's Hospital New Orleans.

Colonic manometry was performed according to a previously published protocol⁸. The subjects were prepared for colon manometry the day before with a colon cleansing regimen. Subjects were sedated prior to colonoscopy for catheter placement. Placement was confirmed using fluoroscopy. The catheter had up to 8 recording sites spaced 10 or 15 cm apart in the colon of each subject. After the subject recovered from anesthesia, we recorded colonic motility for at least 60 minutes during fasting and at least 60 minutes after a meal. Meal content was not standardized: children were allowed to eat as much or as little as they wished of whatever they wanted to eat. Some children refused to eat at all. Thus, meal-stimulated results may have been affected by the subject's post-endoscopy appetite. If there were no HAPCs during the first two hours, we gave bisacodyl 0.2–0.4 mg/kg through the catheter into the right side of the colon and waited one hour for HAPCs. Earlier studies showed the response time to bisacodyl into the right colon averaged 8 min⁷. We recorded colon contractions on a personal computer system (Redtech, Calabassas, CA). Normal colon manometry includes high-amplitude propagating contractions HAPCs which are defined as contractions with amplitude ≥ 60 mmHg, propagating for ≥ 30 cm⁸. We included any contraction over 60 mmHg that propagated for longer than 30 cm measured by colon manometry as an HAPCs even if the contraction did not reach the neorectum. HAPCs are a marker of neuromuscular health. An absence of HAPCs indicates colon neuromuscular disease. We excluded subjects who failed to produce HAPCs during the manometry session in order to exclude patients with severe colonic nerve dysfunction.

We counted HAPCs for each subject while fasting and after a meal. Statistical analysis was performed using GraphPad Prism software 4.0. We performed a multiple comparison ANOVA test comparing the number of HAPCs among groups. Bonferroni's correction was applied in the case of multiple comparisons and a p value of <0.05 was considered statistically significant. The graphs are presented as mean $\pm$ SEM. We ran a paired two-tailed T-test and accepted significance at $p < 0.05$ to determine if the results were consistent with previous data that showed Hirschsprung's subjects have more HAPCs post-prandial than during fasting. We used an unpaired t-test with Welch's correction and accepted significance at $p < 0.05$ to determine if children with Hirschsprung's disease and fecal incontinence ($n=23$) had more HAPCs than those subjects with Hirschsprung's disease and constipation ($n=28$). Results are reported as mean $\pm$ standard error of the mean.

Results

Subjects (n=390) were referred for colon manometry for fecal incontinence, intractable constipation, disabling pain, chronic intestinal pseudo-obstruction, diarrhea, failure to thrive, and after colon transection to determine advisability of restoring continuity. Twenty-four subjects had histories of colonic transection for reasons including intestinal pseudo-obstruction (n=8), intestinal malrotation (n=4), constipation unresponsive to standard medical management (n=8), necrotic bowel removal (n=2), and congenital colon abnormalities (n=2). The colon transection subjects varied in the type of colon surgery, however, most subjects were returning for colon manometries greater than 6 months following transection, and up to 10 years post-transection surgery. In many cases, referring clinicians wanted an assessment of colon motility before a decision about restoration of bowel continuity. Only 2 colon transection subjects presented with symptoms of fecal incontinence (8%) while 12 had constipation symptoms (50%). There were 81 HD subjects with one or more of the following symptoms: fecal incontinence (41%), constipation (50%), or other symptoms including diarrhea or abdominal distention (9%). All the Hirschsprung patients had previously undergone the pull-through procedure as infants. Similar to colon transection subjects, most HD subjects had manometries many years after the surgical procedure for Hirschsprung's disease. There were 237 subjects diagnosed with either functional fecal retention defined by the Rome 2 criteria or functional constipation defined by the Rome 3 criteria. These subjects were initially sent for manometry due to intractable constipation unresponsive to standard of care in the community. 48 subjects referred to manometry had disabling chronic abdominal pain. We excluded 25 HD subjects and 4 colon transection subjects that failed to produce HAPCs. This is noted in figure 1.

After exclusions, we included 361 subjects in the study: 56 HD subjects (age=7.4±5.0yrs; 26 male), 237 subjects with functional constipation (age=6.9±4.1yrs; 144 male), 48 subjects with chronic abdominal pain (age=9.8±5.8yrs; 25 male), and 24 subjects following colon transection (age=6.1±5.8yrs; 12 male). The 361 subjects were divided into 4 groups based on their reason for referral and outcome of colon manometry as shown in Table 1. Symptoms are shown in Table 2. Overall, 57% of the subjects were male and the average age was 7.6±5.1yrs but ranged from <1 to 27 years old. There was no significant age or sex difference among groups.

During fasting there were more HAPCs in HD ($2.2 \pm 3.4/h$) than in functional constipation ($0.80 \pm 2.2/h$, $p=0.0004$) or chronic abdominal pain ($0.46 \pm 1.1/h$, $p=0.001$) (figure 2). After a meal there were more HAPCs in HD ($4.0 \pm 5.4/h$) than in functional constipation ($1.5 \pm 2.5/h$, $p < 0.0001$) or chronic pain ($0.93 \pm 1.6/h$, $p < 0.0001$) (figure 3). There was no significant difference in HAPCs between HD ($2.2 \pm 3.4/h$ and $4.0 \pm 5.4/h$) and the colon transection group ($1.9 \pm 3.2/h$, $p=0.2$ and $2.4 \pm 3.0/h$, $p=0.8$) during fasting or after a meal.

When we combined all subjects that underwent colon transection, including Hirschsprung's disease subjects, and compared those subjects to those with functional constipation and chronic pain combined we found a two fold increase ($p < 0.0001$) in the number of fasting HAPCs and a two fold increase ($p < 0.0001$) in the number of post-prandial HAPCs between the groups (figure 4).

HD subjects with fecal incontinence only had more HAPCS fasting and post-prandial ($3.8 \pm 4.1/h$, $p=0.01$ and $6.4 \pm 6.6/h$, $p=0.01$) compared to children with HD and constipation ($1.2 \pm 2.8/h$ and $2.2 \pm 4.0/h$) (figure 5). HD subjects with constipation only had similar number of HAPCs fasting and post-prandial ($1.2 \pm 2.8/h$, $p=0.5$ and $0.8 \pm 2.2/h$, $p=0.4$) compared to subjects with functional constipation ($0.80 \pm 2.2/h$ and $1.5 \pm 2.5/h$) and subjects with chronic pain ($0.46 \pm 1.1/h$ and $0.93 \pm 1.6/h$). HAPC numbers did not correlate with length of remaining colon (figure 6).

Discussion

A majority of HD patients have defecation disorders after successful surgery. There are three distinct groups who come to attention. Many are children with incontinence due to too many HAPCs through the neorectum to the anal verge. A second group is children with continuing constipation and absent HAPCs, suggesting a neuropathy proximal to the aganglionic segment. It is worth noting that neuropathic motility abnormalities are seen in HD in esophagus, stomach, and small bowel of adults with HD treated in childhood¹²¹³. Therefore, it should come as no surprise that symptoms arise from motility problems in the remaining, presumably healthy colon. A third group of HD children have constipation with colon motility that is no different than children with functional constipation. The symptoms arise from failure to relax the muscles involved in defecation. In some of the constipated children with normal colon motility there may be a problem with involuntary failed relaxation in the anal sphincter, a consequence of HD⁵. In others, early life painful or scary experiences with defecation may have discouraged the child from defecation, and the diagnosis is functional constipation: failed pelvic floor relaxation because the child chooses to avoid defecation. Finally, some children have no problems with defecation after HD surgery. It seems plausible that problems after successful surgery may be related to the type of mutation responsible for the disease. Different HD genotypes may present with phenotypic differences¹⁴¹⁵.

HD subjects and colon transection subjects had more HAPCs than subjects with functional constipation or chronic abdominal pain, suggesting that colon transection up-regulated HAPCs. In previous studies, adult patients undergoing sigmoid colon and rectal transection due to rectal cancer also presented with increased colon activity upon barostat testing¹⁶. This up-regulation could be attributed to a loss of inhibitory tone, or an increase in excitatory factors. During transection surgery, dissection of the extrinsic nerve accompanying the inferior mesenteric artery is generally required, causing section of some of the sympathetic nerves running along the same length of the gut¹⁷. This offers a possible explanation for the disappearance of an inhibitory effect on colon motility. Perhaps, the group of HD subjects that later develop fecal incontinence after transection develop additional abnormal neural connections in their proximal colon that lead to the production more HAPCs. These patients that experience HD and excess HAPCs may also have a phenotypic variation of Hirschsprung's disease. Colon transection up regulates HAPCs and coupled with phenotypic variation of HD may factor into why these patients develop fecal incontinence and increase HAPCs.

Results from subjects with functional constipation and chronic abdominal pain were similar. Although there has never been a colon manometry study of normal children, it seems a fair assumption that these two conditions serve as control population. In the present study HD children with HAPCs and a chief complaint of constipation had HAPC numbers similar to those of subjects with functional constipation and chronic abdominal pain. Therefore, HD children with HAPCs and constipation as a chief complaint may have functional constipation. That is, a frightening or painful defecation experience in their past caused them to avoid defecation by failing to relax the pelvic floor in response to HAPCs.

In Hirschsprung's disease increased HAPCs correlated with fecal incontinence, a socially undesirable problem for children. Clinical management of children with fecal incontinence following surgery usually involves treatment with anti-cholinergic medicines to slow colonic transit time¹⁸. Understanding the cause for increased HAPCs could lead to better treatment.

There were a number of limitations to this retrospective study. First, data were accrued at 4 different motility centers (although the senior author was present at all the sites). Second, anesthesia changed during data accrual, from narcotics and benzodiazepines to benzodiazepines and propofol. As a consequence, post anesthesia recoveries prior to starting manometry were reduced from 3 hours (after narcotics) to as little as 90 min after propofol.

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Figure 1.
Colon manometry diagnostic results

Figure 2.

Average number of HAPCs recorded during fasting. * $p = 0.001$, ** $p = 0.0004$. Results are mean $\pm$ standard error of the mean.

Figure 3. Average number of HAPCs recorded during the post-prandial period. * $p < 0.0001$. Results are mean $\pm$ standard error of the mean.

Figure 4.

Comparison of HAPCs between groups that underwent colon transection (including Hirschsprung's disease subjects) vs. functional constipation and chronic pain. * $p < 0.0001$.

Results are mean $\pm$ standard error of the mean.

Figure 5.

Comparison of HAPCs fasting and post-prandial between Hirschsprung's children presenting with fecal incontinence vs. Hirschsprung's children presenting with constipation.

* $p=0.01$, ** $p=0.01$. Results are mean $\pm$ standard error of the mean.

Figure 6.

Comparison of HAPCs between Hirschsprung's subjects presenting with constipation vs. functional constipation and chronic abdominal pain. p is not significant.

Table 1

Subject characteristics. Age is mean $\pm$ SD.

	age	males	females	total
Hirschsprung's disease	6.9 $\pm$ 4.1yrs range=<1–17	44	12	56 (16%)
colon transection	6.1 $\pm$ 5.8yrs range=<1–19	12	8	20 (5%)
no colon disease	9.8 $\pm$ 5.8yrs range=<1–26	25	23	48 (13%)
functional constipation	7.4 $\pm$ 5.0yrs range=<1–27)	126	111	237 (66%)
TOTAL	7.6 $\pm$ 5.1yrs	207 (57%)	154(43%)	361

Table 2
Symptoms in subjects. Numbers in parenthesis indicate percent of subjects with each symptom.

	constipation fecal	constipation fecal	constipation fecal	constipation fecal
Hirschsprung's disease	Hirschsprung's disease	Hirschsprung's disease	Hirschsprung's disease	Hirschsprung's disease
28 (50%) 23 (42%) 1 (2%) 0 2(4%) 2 (4%)	28 (50%) 23 (42%) 1 (2%) 0 2(4%) 2 (4%)	28 (50%) 23 (42%) 1 (2%) 0 2(4%) 2 (4%)	28 (50%) 23 (42%) 1 (2%) 0 2(4%) 2 (4%)	28 (50%) 23 (42%) 1 (2%) 0 2(4%) 2 (4%)
colon transection	colon transection	colon transection	colon transection	colon transection
13 (65%) 1 (5%) 0 2 (10%) 0 4 (20%)	13 (65%) 1 (5%) 0 2 (10%) 0 4 (20%)	13 (65%) 1 (5%) 0 2 (10%) 0 4 (20%)	13 (65%) 1 (5%) 0 2 (10%) 0 4 (20%)	13 (65%) 1 (5%) 0 2 (10%) 0 4 (20%)