Functional defecation disorders in children
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Chapter seven

CHARACTERIZING COLONIC MOTILITY IN CHILDREN WITH CHRONIC INTRACTABLE CONSTIPATION

A look beyond high-amplitude propagating sequences

S. Kuizenga-Wessel, I.J.N. Koppen, L. Wiklendt, M. Costa, M.A. Benninga, P.G. Dinning

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ABSTRACT

Background: Children with chronic intractable constipation experience severe and long-lasting symptoms, which respond poorly to conventional therapeutic strategies. Detailed characterization of colonic motor patterns in such children has not yet been obtained. Methods: In 18 children with chronic intractable constipation, a high-resolution water-perfused manometry catheter (36 sensors at 1.5cm intervals) was colonoscopically placed with the tip at the distal transverse colon. Colonic motor patterns were recorded for 2 hours prior to and after a meal, and then after colonic infusion of bisacodyl. These data were compared to previously published colonic manometry data from 12 healthy adult controls and 14 adults with slow transit constipation.

Key results: The postprandial number of the retrograde cyclic propagating motor pattern was significantly reduced in these children compared to healthy adults (children; 3.1 ± 4.7/hr vs healthy adults 34.7 ± 45.8/hr; P < 0.0001) but not constipated adults (4.5 ± 5.6/hr; P = 0.9). The number of preprandial long single motor patterns was significantly higher (P = 0.003) in children (8.0 ± 13.2/hr) than in healthy adults (0.4 ± 0.9/hr) and constipated adults (0.4 ± 0.7/hr). Postprandial high-amplitude propagating sequences (HAPS) were rarely observed in children (2/18), but HAPS could be induced by bisacodyl in 16/18.

Conclusions and inferences: Children with chronic intractable constipation show a similar impaired postprandial colonic response to that seen in adults with slow transit constipation. Children may have attenuated extrinsic parasympathetic inputs to the colon associated with an increased incidence of spontaneous long single motor patterns.
INTRODUCTION

Functional constipation is a common pediatric healthcare problem with a worldwide prevalence ranging from 0.7% to 29.6%\(^1\). It is estimated to account for 3% of general pediatrician visits and up to 25% of visits to a pediatric gastroenterologist in the United States\(^1\). A subtype of children with delayed colonic transit, can suffer from severe and long-lasting symptoms, which usually respond poorly to conventional therapeutic strategies\(^1\), and result in a significant impact on the child’s quality of life\(^2\)-\(^6\),\(^1\)\(^6\)-\(^8\). When symptoms are irresponsive to optimal conventional treatment for at least 3 months, this is referred to as intractable\(^4\). In severe cases, children with chronic intractable constipation may require surgical interventions such as an ileostomy or a (sub)total colectomy\(^9\)-\(^9\). Although the pathophysiology of constipation is incompletely understood, abnormalities in the contractile activity of the colon are implicated to play an important role\(^1\)\(^0\),\(^1\)\(^1\),\(^1\)\(^0\). Several studies have used low-resolution colonic manometry to record contractile activity in children with constipation, commonly reporting a reduced frequency of high amplitude propagating sequences and an absent or diminished meal response\(^5\),\(^7\),\(^9\). Such findings indicate that a potential colonic neuropathy may exist. More recently, studies utilizing high-resolution manometry have emerged\(^1\)\(^2\),\(^1\)\(^2\). In one of these studies, colonic manometry was performed prior to (partial) colectomy in severely constipated children\(^1\)\(^2\). This study provided manometric evidence of a neuropathy by showing that the normal suppression of motor activity between bisacodyl induced high amplitude propagating sequences, did not occur in a sub-group of constipated children with neurogenic abnormalities confirmed on histological examination of their removed colonic tissue.

Recently, high-resolution colonic manometry was used to provide a detailed characterization of propagating motor patterns prior to and after a meal in healthy adults\(^1\)\(^3\). One of the key findings was a postprandial increase in retrograde cyclic propagating motor patterns in the distal colon, comprising of pressure events with a slow wave frequency of 2-6 per minute\(^1\)\(^3\). The rapid increase in this motor pattern after a meal (within 1 minute of starting to eat) suggests that it is influenced by extrinsic neural input\(^1\)\(^3\). This postprandial response was absent in adult patients with slow transit constipation, leading the authors to hypothesize the existence of a possible neuropathy in the extrinsic parasympathetic innervation of the colon in these constipated adults\(^1\)\(^0\).

Whether or not such motor pattern abnormalities exist in children with chronic intractable constipation has not yet been established. Therefore, in this study, our aim was to quantify the colonic motor patterns in such children, utilizing
high resolution colonic manometry. These data were then compared to the previously published manometric findings from healthy adults and adults with slow transit constipation\(^{10,123}\). Specifically, we hypothesized that both children and adults with intractable constipation would display similar motor abnormalities prior to and after a meal, indicating that the potential neuropathy identified in adults is also present in children.

**METHODS**

**Study population**

All children scheduled for colonic manometry for evaluation of chronic intractable functional constipation at our tertiary referral center (Emma Children’s Hospital / Academic Medical Center, Amsterdam, the Netherlands) between January 2014 and June 2015, were potentially eligible for the study. Children with intractable constipation underwent colonic manometry as part of standard care. Children had to meet the following criteria for inclusion; **a)** fulfilled the Rome III criteria for functional constipation\(^{124}\); **b)** aged between 0 – 18; **c)** failed response to intensive treatment (high dosage osmotic and stimulant laxatives, colonic lavage). Patients were excluded if they had constipation with a known organic cause.

Colonic transit studies were not routinely performed in these children. Many parents were reluctant to allow their children to stop taking medications to allow a transit study to be conducted out of fear for deterioration of symptoms. As such colonic transit was only measured in nine children. We adopted a radiopaque marker study where a capsule with 10 radio opaque markers was ingested on 6 consecutive days with an abdominal X-ray on day 7. Colonic transit time was calculated by multiplying the number of intra-abdominal markers by the constant 2.4. The 2.4 represents the ratio between the period in which the examination was performed (144 hours) and the number of markers ingested (n = 60)\(^{125}\).

Ano-rectal manometry studies were performed in 13 of the 18 children. As with the colonic transit studies, some parents were reluctant for their children to undergo this test. In this procedure anal squeeze and resting pressures were measured as was the presence of a rectoanal inhibitory reflex (RAIR).

All adults were recruited and studied at Flinders Medical Centre, Adelaide, South Australia, Australia. The recruitment of healthy adults has been described elsewhere\(^{123}\). In summary, subjects had to be aged 19-75 years and had normal bowel habits, defined as having between three bowel movements a day and
one bowel movement every three days, with no symptoms of rectal evacuatory difficulty or other gastrointestinal symptoms. All adult participants gave written, informed consent and the studies were approved by the Human Ethics Committees of the South Eastern Area Health Service, Sydney and the University of New South Wales (05/122; May 2010), and The Southern Adelaide Health Service/Flinders University Human Research Ethics Committee (419.10; March 2011). The inclusion and exclusion criteria for the adult constipated patients have been provided in detail previously. Briefly, all patients were 19-75 years of age, had slow transit constipation confirmed scintigraphically, normal anorectal function and had failed symptomatic response to standard constipation therapies. Patients were excluded if they had metabolic, other neurological or endocrine disorder(s) known to cause constipation, had prior abdominal radiotherapy, current or planned pregnancy.

**Colonic catheters and recording setup**

In all children, a high-resolution water-perfused manometry catheter with 36 pressure sensors each spaced at 1.5cm intervals was used (MMS, Netherlands, stationary manometry version 9.3K). The lumina were perfused with distilled water (0.15 ml/min). Intestinal intraluminal pressures were recorded by external pressure transducers and pressure signals were digitized and stored on a computer. In all adults, colonic pressures were recorded with a 72 sensor (spaced 1cm apart) high-resolution fiber-optic manometry catheter. The fiber-optic catheters were attached to a spectral interrogator unit (FBG-scan 804; FOS&S, Geel, Belgium) and pressures were recorded in real time on a custom-written LabVIEW© program (National Instruments, Austin, Texas, USA).

**Colonoscopic placement of the catheter**

Pediatric patients were admitted to the hospital prior to the manometry for colonic lavage with either Klean-Prep® or PicoPrep®, administered according to standard hospital procedures. The colonic lavage protocol was tailored to individual needs if necessary by increasing the number of days or dosage of laxatives. Children received a clear liquid diet starting 24 hours before the colonoscopy and fasted overnight. Colonoscopy was performed under general anesthesia with Diprivan (dose varied depending based on body weight). A suture loop was tied to the tip of the catheter and covered with Parafilm M®. This loop was held by a snare passed through the biopsy channel of the colonoscope. With the aid of the colonoscope the catheter tip was introduced into the distal transverse colon to ensure there were recording sites spanning the descending and sigmoid colon. The suture loop was clipped to the mucosa of
the transverse colon using hemostatic clips (Resolution Clip; Boston Scientific Corporation; Marlborough, MA). The position of the catheter and any migration during the manometry were determined by abdominal X-ray prior to initiation (directly after placement of the catheter) and after completion of the manometry recording (Figure 1).

For the adult studies, catheter placement has been described elsewhere\textsuperscript{110,123}. In adults, the catheter tip was placed in the ascending or proximal transverse colon. For this study only the data recorded from the descending and sigmoid colon were considered.

**Manometry Protocol**

The manometry protocol in children was similar to the protocol used in adults\textsuperscript{110,123,60}, with a few notable exceptions. In adults, because lighter levels of sedation were used, colonic manometry recording commenced within 60 minutes after catheter placement. In the children, the recording started within 2-4 hours after catheter placement, to ensure children were fully awake. In adults, a set meal, containing 700 kCal was consumed. In children, the calorie content of the meals differed depending on the age of the child (<12 years: minimum 400kcal, ≥12 years: minimum 700kcal).

In all subjects colonic manometry was recorded for 2 hours in the basal fasting state, followed by a further 2 hours after a meal. Then, only in children, after 4 hours of recording, bisacodyl (Bisacodyl, Boehringer Ingelheim BV, Alkmaar, The Netherlands) was introduced into the colon via the central lumen of the catheter. The bisacodyl dose varied depending upon body weight (<50 kg: 5mg, ≥50 kg: 10mg bisacodyl). Afterwards, the recording continued for another hour. If the first dose did not induce high-amplitude propagated sequences (HAPS) within 30 minutes, a second dose of bisacodyl (twice the initial dose; 10 or 20 mg) was administered and the recording continued for an additional 30-60 minutes (until HAPS were observed).

**Analysis of manometric data**

**Manual Analysis**

All analyses of manometric data were performed using software (PlotHRM) developed by one of the authors (LW). PlotHRM was written in Matlab\textsuperscript{©} (The MathWorks, Natick, Massachusetts, USA) and Java\textsuperscript{TM} (Sun Microsystems, Santa Clara, California, USA).

In each manometry tracing, artifacts and simultaneous pressure events that spanned all recording channels were digitally removed as described previously\textsuperscript{110,123}. Each of the pressure traces was then visually inspected by one of the
authors (PD) for propagating activity; defined as pressure events that occurred in ≥4 adjacent channels in the fiber-optic data and ≥3 in the water-perfused data (i.e. ≥ 3 cm in both data sets). If a pressure event returned to baseline before the pressure event in the adjacent channels started, then the two events were not considered part of the same propagating motor pattern. Propagating motor patterns were classified on the basis of whether they occurred cyclically or as single events, whether their propagation was anterograde (anally-propagating) or retrograde (orally-propagating), by their propagation velocity and by the distance over which they travelled.

In the previously published data of colonic motor patterns recorded in healthy adults, four commonly seen and distinct propagating motor patterns were defined;
A) High amplitude propagating sequences (HAPS). Consistent with previous studies, these propagating motor patterns consisted of an array of pressure events with the majority having a trough-to-peak amplitude of >116 mmHg and always progressed in an antegrade direction.

B) Cyclic motor patterns. Repetitive propagating pressure events with cyclic frequency of 2-6 cycles per minute occurred in all healthy adults. These motor patterns propagated in either retrograde or antegrade direction.

C) Short single motor patterns. This pattern occurred in isolation separated from other propagating motor patterns by intervals of more than 1 minute. They could propagate in a retrograde or anterograde direction.

D) Long single motor patterns; these occurred as single pressure events which propagated over long distances. These motor patterns were always separated by intervals of more than 1 minute, when they occurred repetitively. In all instances these motor patterns comprised of pressure events recorded in every pressure sensor (i.e. they spanned the entire recording region).

Spectral analysis of colonic pressure wave data
Welch’s method was used to calculate a periodogram on the raw data from the pediatric patients. This analysis determines the dominant frequencies of pressure events. For each subject, the root mean square (RMS) amplitude of frequencies of pressure time-series (range; 0.15-8 cycles per minute (cpm); increasing at increments of 0.15 cpm) was averaged over each individual channel in each of the colonic regions; in this instance the descending and sigmoid colon.

Statistical analysis
All data are expressed as mean ± SD. The average number, velocity (speed of propagation), extent (distance of propagation) and amplitude of each type of propagating motor patterns were all calculated in PlotHRM. For the pediatric data the non-parametric Wilcoxon signed rank test was used to compare these propagation characteristics between the basal and postprandial periods. The analysis of the adult data has been published previously. Comparisons between the number of propagating motor patterns in the pediatric data and both adult groups was performed with Kruskal-Wallis test of One-way ANOVA, with Dunn’s correction for multiple comparisons. As the data in children and adults were recorded with two different catheters (water-perfused and fiber-optic) no attempt was made to calculate differences in amplitude between children and adults. All statistics were calculated using Prism 5 (GraphPad Software, Inc., La Jolla, CA, USA). A p-value <0.05 was considered statistically significant.
Frequency spectra were analyzed using a Bayesian estimation method based on statistical modeling using the t-distribution. We utilized the Markov chain Monte Carlo (MCMC) technique using software from the Stan Development Team (PyStan: the Python interface to Stan. Version 2.4). Analysis of t-distributions was chosen because it is a robust approach to handle outliers. We have used the MCMC technique in previous publications, where the technique is described in detail.\textsuperscript{10,12,13}

Here, the mean RMS distribution for each frequency and patient type is computed with MCMC.

Statistical differences between the grouped means between preprandial and postprandial data within pediatric subjects were then calculated. This was achieved by subtracting the preprandial means from the postprandial means. Where the 95% highest density interval of the differences between the means being compared did not contain a 0 (i.e. the value was greater than 0) there was considered to be a statistically significant difference. The greater the value from 0, the greater the effect size.

\textbf{RESULTS}

Colonic manometry was performed in 19 children (median age 15 years; range 4-18 years). In one of the subjects the catheter tip was placed in the cecum, which resulted in manometric recordings from the ascending colon, the transverse colon and proximal the descending colon only. The data of this patient have been excluded from all analyses; leaving 18 patients (5 males). In one child (no.12, Table 1) all of the sensors were located in the sigmoid colon. Thus, data for descending colon are reported from 17 children. Of the nine children with measured colonic transit 6 had proven slow transit constipation and the remaining 3 had normal colonic transit (Table 1). However, in the children diagnosed with “normal transit” laxative medication was taken.

Of 13 children that had anorectal manometry, 11 had demonstrable evidence of a rectoanal inhibitory reflex (RAIR) and normal or slightly elevated anal sphincter resting pressure (Table 1). The remaining two children did not have manometric evidence of RAIR. However, both children have since had Hirschsprung’s disease excluded from their pathology.

The adult data came from 14 patients with scintigraphy-diagnosed slow transit constipation (2 men; median age 52 years; range 24-76 years) and 12 healthy adults (5 men; median age 51 years; range 27-69 years)\textsuperscript{110,123}.

The patients with slow transit constipation all reported a long history of
constipation with 10 out of 14 patients reporting constipation from childhood and
the remaining 4 reporting constipation worsening from puberty into adulthood.

1) Spectral Analysis
In comparison to the adult data, the pediatric data showed very little
evidence of cyclic activity of 2-3 cpm prior to, or after the meal in either
region of the colon (Figure 2). In addition, in contrast to healthy adults, there
was no increase in colonic pressure events in the pediatric patient group
after the meal.

2) Propagating Motor Patterns
At least one type of propagating motor pattern was identified in each of the
children (Table 1). The average count, velocity, amplitude and extent of prop-
agation of each type of propagating motor pattern are shown in Table 2.
Apparent non-propagating and random pressure events were also recorded
in all children (Fig 3A). In children, the meal did not significantly increase any
parameter for any of the propagating motor patterns (Figure 4; Table 2).
Prior to the meal there was no significant difference amongst the groups
(children, healthy adults and constipated adults) in the number of ante-
grade/retrograde cyclic motor patterns or antegrade/retrograde short single
motor patterns (Fig 4 A-D). After the meal there was a significant difference
amongst the groups in the number of the retrograde cyclic motor pattern
(p<0.0001). The postprandial increase in this motor pattern in healthy adults
was not observed in either patient group10,123
Indeed, in 8 (44%) children this motor pattern was not observed in the post-
prandial period (Table 2). In the remaining 10 children it occurred in small
numbers (1-9/hr; Figure 4B). As a result there was a significantly greater
number of the retrograde cyclic motor patterns in healthy adults (34.7 ±
45.8/hr) compared to the children (3.1 ± 4.7/hr; p<0.0001). The number of this
motor patterns did not differ between the constipated children and adults
(3.1 ± 4.7/hr vs 4.5 ± 5.6/hr; p=0.9)
The other notable difference between the groups was the number of long
single propagating motor patterns prior to the meal (p=0.0006; Figure 3 &
4E). This was due to a higher number of these motor patterns in children
compared to both healthy and constipated adults. During the preprandial
recording, the number of long single propagating motor patterns in chil-
dren (8.0 ± 13.3/hr; range 0-54/hr; Figure 4E) was significantly greater than
in healthy adults (0.4 ± 0.9/hr; range 0-3; p=0.005) and in constipated adults
(0.4 ± 0.7/hr; range 0-2; p=0.003). The postprandial number of these motor
patterns was significantly lower in children (0.0 ± 0.0/hr; range 0-1; p=0.003) than
in healthy adults (1.3 ± 10.1/hr; range 0-100/hr; p<0.0001). This increase in
motor activity was also significantly greater (p<0.0001) in healthy adults
than in constipated adults (4.5 ± 5.6/hr vs 2.0 ± 1.0/hr; p=0.0003). In children
the meal did not significantly increase any parameter for the retrograde
cyclic motor patterns, endocyclic (p=0.007; Figure 4F) or transitional
(p=0.008; Figure 4G).

166
Colonic motility patterns also differed amongst the 3 groups \((p=0.04)\). Again the children \((10.3 \pm 15.6/hr; \text{range } 0-61/hr; \text{Figure } 4E)\) had more of these motor patterns than either of the adult groups \((\text{health } 1.5 \pm 1.8/hr; \text{range } 0-6/hr; \text{constipation } 1.8 \pm 2.9/hr; \text{range } 0-10/hr)\), however, with correction for multiple comparisons no individual statistical difference was found. In one of the children \((\text{no.16; Table 1})\) the long single motor pattern continued at a frequency of ~1.2 cpm throughout the entire pre- and postprandial period \((\text{Figure } 3B)\). No other propagating motor patterns were recorded in this child until the bisacodyl infusion \((\text{see below})\).

3) Spontaneous and meal-induced HAPS

HAPS were identified in one child prior to the meal \((\text{no.12})\) and in 2 children after the meal \((\text{no.9 & 12, Table 1})\). In the child with all the sensors located in the sigmoid colon \((\text{no.12; Table 1})\), the high amplitude pressure peaks propagated through the proximal regions of the sigmoid colon and then stopped \((\text{Figure } 5)\). This same pattern was observed in this child during the postprandial recording and during bisacodyl infusion \((\text{see below & Figure } 6)\). In the other child \((\text{no. 9})\) the postprandial HAPS were observed to extend over the descending and sigmoid colon, terminating at the top of the rectum. As previously reported\(^{123}\) these motor patterns were only identified in one adult with slow transit constipation and in 6 of the 12 healthy adults. In adults, the HAPS were only recorded in the postprandial phase and not in the preprandial phase.

4) Colonic response to bisacodyl

After administration of bisacodyl, HAPS were initiated in 16 out of 18 children \((\text{Table 1})\). The first HAPS was recorded 4.3 ± 2.3 minutes \((\text{range } 1.1-7.9 \text{ minutes})\) after bisacodyl infusion, and there was an average count of 10.1 ± 4.6; range 2-19. Defecation occurred after bisacodyl infusion in 14 out of 18 children. In two children \((\text{no.4 & 14; Table 1})\) HAPS were recorded in the absence of defecation, whilst in another \((\text{no.3, Table 1})\) defecation occurred without HAPS. An absence of defecation and HAPS was only observed in one child \((\text{no.18; Table 1})\).

In the child with the repetitive long single motor patterns \((\text{no.16; Table 1})\) a strong colonic response was recorded in response to bisacodyl, with 15 HAPS recorded in a 22-minute period. In child no. 12 \((\text{Table 1})\), bisacodyl infusion induced a series of HAPS which all terminated at the same location as the spontaneous HAPS \((\text{Figures } 5&6)\).
Table 1  The propagating motor patterns identified in each of the subject prior to and after the meal and in response to colonic infusion of bisacodyl

<table>
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<th>Subject</th>
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F: female, M: male (age in years); HAPS: High amplitude propagating sequence; Cyclic: propagating motor pattern; Short single: propagating motor pattern; Long single: propagating motor pattern; 1 Slow transit constipation; 2 Normal colonic transit. Laxatives were taken during the transit studies; ▲ normal ano-rectal manometry; □ absent recto-anal inhibitory reflect (ano-rectal manometry); * Defecation occurred after Bisacodyl infusion
Table 2. Characteristics of propagating motor patterns in the ascending and sigmoid colon in the children, healthy adults (HA) and adults with slow transit constipation (STC). Data are shown for one hour prior to the meal and the one hour from the start of the meal.

<table>
<thead>
<tr>
<th>Count</th>
<th>PREPRANDIAL</th>
<th>POSTPRANDIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Antegrade</td>
<td>Retrograde</td>
</tr>
<tr>
<td>Child</td>
<td>22 ± 35</td>
<td>18 ± 29</td>
</tr>
<tr>
<td>HA</td>
<td>35 ± 69</td>
<td>35 ± 85</td>
</tr>
<tr>
<td>STC</td>
<td>20 ± 54</td>
<td>30 ± 53</td>
</tr>
</tbody>
</table>

* Count significantly greater in healthy adults than children (p value shown in table).
Spectral analysis of pressure events in the descending colon (top) and sigmoid colon (bottom), before the meal (A) and after a meal (B), in children (green), adults with slow transit constipation (red) and healthy adults (blue). The X-axis represents the frequency (cycles per minute) of recorded pressure events and the Y-axis is the root mean square (RMS) of these pressure spectra (amplitude). The green, blue and red shaded regions represent the distribution of means over each subject group. The solid green, red and blue lines in (B; top and bottom) represent the lower edge of the 95% highest density interval of the differences of means between the pre- and postprandial data. Where the solid colored lines appear above 0 (i.e. above the solid black line in each image) a significant different is observed. In both the descending and sigmoid colon the green line does not appear above 0 indicating that the meal has no significant effect on the colonic activity in these children. In healthy adults the solid blue line appears above 0 at all frequencies. Note the pre- and postprandial spike in 2-3cpm activity in the sigmoid colon of both adult groups. This activity is not evident in the children.
A) Typical motor patterns recorded in the constipated children. Note that within the sigmoid colon there are multiple motor patterns recorded but very few appear to propagate in any direction. In this example 4 long single propagating motor patterns can be seen. The start of each one is shown by the black arrows. B) The motor pattern recorded throughout the pre- and postprandial period in Child no. 16 (see table 1). In this child long single motor patterns (black arrows) were identified prior to and after the meal at frequency of ~1.2cpm.
The count per hour of A & B) cyclic, C & D) short single and E) long single propagating motor patterns. The children are shown in green, healthy adults in blue and adult patients with slow transit constipation shown in red. The closed shapes of each color represent the preprandial data and the open shapes the postprandial data. The meal did not increase the count of any motor pattern in children. There was a significant difference \( (p < 0.0001) \) in the count of the retrograde cyclic motor patterns after the meal amongst the three groups, with an increase in this motor noted in health but neither of the patient groups. There was also a significant difference in the pre- and postprandial count of long-single motor patterns \( (P = 0.0006 \ & P = 0.04, \text{ respectively}) \) with a greater number recorded in children than the two adult groups. Note the difference in the scale of the Y-axis for the cyclic, short and long single motor patterns.
Spontaneous high amplitude propagating sequence (HAPS) recorded during prior to the meal in child No. 12 (Table 1). In this child all of the recording sensors where located in the sigmoid colon. The black oval shapes outline the location of every 2nd sensor. The high amplitude propagating sequence terminated at 17 (Black circle on the manometry trace). The post-prandial HAPS in this child and the bisacodyl induced ones (see Fig 6) all terminated at this same location.

Bisacodyl induced high amplitude propagating sequences (HAPS) induced in child No. 12. These chemically induced HAPS all terminated at the same location (solid black circle) as the spontaneous one shown in Fig 5. Despite the initiation of these motor patterns the child did not defecate.
DISCUSSION

In this study, utilizing high-resolution water-perfused manometry we have quantified the motor patterns of the descending and sigmoid colon in children with chronic intractable constipation. Our data confirm the finding of previous adult studies, that these children lack a normal meal response\textsuperscript{59,128}. In addition we demonstrate that in most subjects (16/18), HAPS were initiated by colonic infusion of bisacodyl. Spontaneous HAPS were only observed in 2/18 children. When these data are compared to fiber-optic high-resolution manometry recorded in healthy adults\textsuperscript{123} and adults with slow transit constipation\textsuperscript{110}, several keys point emerge; 1) All four major colonic motor patterns described in healthy adults were present in the constipated children; 2) the constipated children have a smaller number of motor patterns with 2-4 cycle per minute (propagating or non-propagating) than either of the adult groups (Figure 2); 3) the number of long-single propagating motor patterns recorded in children during the fasted period is significantly greater than in either adult group; 4) the number of postprandial propagating events of any kind does not differ between constipated children and adults; 5) the increase in the postprandial cyclic motor patterns present in healthy adults is absent in these children, as is also seen in constipated adults.

High amplitude propagating sequences

Traditionally colonic manometry studies have focused mainly upon the presence, amplitude and frequency of HAPS. These motor patterns are considered the main driving force behind the antegrade mass movement of feces\textsuperscript{127} by peristaltic contractions mediated by enteric neural circuits and are associated with spontaneous\textsuperscript{128} and chemically induced \textsuperscript{129} defecation. The presence of HAPS during colonic manometry, either spontaneous or after bisacodyl provocation, is therefore of importance in determining normal colonic propulsive contractions dependent on enteric neural mechanisms. Indeed the presence of these motor patterns is used to confirm normal colonic motility, and thus to predict success of antegrade enemas through an appendicostomy or cecostomy or to help making decisions in (surgical) management\textsuperscript{57,130}.

In this study only 2/18 children showed spontaneous HAPS. While this could be seen as evidence of a potential neuropathy\textsuperscript{121}, it is also important to note that HAPS were only observed in half of healthy adults. As we have argued previously\textsuperscript{223} the relative paucity of this motor pattern in many of our healthy controls may result from our current protocol. By recording in an empty colon we are likely to have removed one of the major stimuli to induce this motor
pattern. In animal preparations, distension of the colon initiates propulsive peristaltic contractions mediated by enteric neural circuits, with the speed of propulsion dependent on the size of the bolus. Therefore absence of HAPS in an empty human colon does not necessarily imply abnormality.

For this reason a more appropriate test of normal propulsive function due to normal enteric neural mechanisms is the challenge with bisacodyl. After administration of bisacodyl, HAPS were identified in 16/18 children, indicating that the mechanisms involved in the chemical initiation of these motor patterns is present in most subjects. Thus, although this finding does not mean that these children have normal colonic motility, it suggests that the enteric neural circuits responsible for the chemically triggered peristaltic contractions are functioning normally.

One of the advantages of high-resolution manometry is that we are now able to characterize many more propagating motor patterns, than we could previously identify using the low resolution recordings. In our high-resolution manometry work in healthy adults we were able to statistically identify two distinct groups of propagating motor patterns, on the basis of the shape of the component pressure events. The first group included the HAPS and these were classified as neurogenic because they require a luminal stimulus and/or extrinsic neural input for their generation. The second group consisted of all other propagating motor patterns (cyclic, short and long single motor patterns). Since the cyclic motor pattern consisted of pressure events with a frequency of 2-6cpm, and corresponds to the smooth muscle slow waves, known to be generated by the pacemaker system responsible for the smooth muscle slow waves, these motor patterns were classified as myogenic (i.e. they are initiated within the muscle). These myogenic motor patterns made up 98% of all propagating activity in healthy adults and appears to be under significant extrinsic nerve influence. In this current study it is this myogenic motor pattern that shows the most striking differences between the patients and healthy adults.

**Colonic Meal Response**

The normal distal colonic increase in propagating cyclic motor patterns observed after a meal in healthy adults was not seen in these children. The rapid increase in their incidence after a meal has been taken as evidence that these myogenic motor patterns are influenced by extrinsic neural inputs. Neurally mediated feeding response of the colon in experimental animals is a well known. A lack of increase of this motor pattern after a meal was also observed in adult patients with slow transit constipation, leading us to
speculate that a neuropathy of the extrinsic parasympathetic inputs to the colon may be the cause. This may also be the case in our constipated children. It cannot be excluded that the abnormality lies within the pacemaker system of ICCs because in 8/18 children the cyclic propagating motor pattern was absent prior to or after the meal and in all children the recorded pressure events appeared, at times, in a non-propagating and chaotic fashion (Fig 3A). The low number or even absence of the cyclic motor pattern was more notable in constipated children than in constipated adults. While there may be some methodological explanations for this difference (see section on potential limitations below), the question remains as to why this would be the case. While the motor patterns may change with age, an equally plausible explanation is that the neuronal lesions in these constipated children may be more severe.

Based on colonic manometry results, 5 of them have had ileostomies fashioned and 2 have had a subtotal colectomy. Therefore some of these severely constipated children may be treated surgically long before they would be seen as adult patients. This suggests that these children had a preexisting more serious morbidity. Different therapeutic strategies were used in the remaining 12 children (high dosage of oral laxatives, n=1; sacral neuromodulation, n=3; daily transanal colonic irrigation, n=5; Kleanprep combined with daily transanal colonic irrigation, n=3)

Long Single Motor Pattern

Long single propagating motor patterns travel rapidly in an antegrade direction across all of the recording sites that span the descending and sigmoid colon (in health, they originate in the proximal colon\textsuperscript{123}). The specific physiological role of this motor pattern is unknown. However, given the low amplitude of the component pressure events and its speed of propagation, it would be unlikely to propel solid content through the colon. This motor pattern was more prevalent in the children than either of the adult groups and the question arises as to why this occurred. Although the pressure events that make up these motor patterns cannot be distinguished by shape from those that make up the cyclic motor patterns, it is possible that they are due to intrinsic neural activity\textsuperscript{123}. There is increasing evidence that within the small intestine and in the colon of most mammalian species studied, in addition to the content dependent propulsive peristaltic contractions (corresponding to the HAPS in humans), there are enteric circuits that generate spontaneous cyclic motor activity at intervals of about a minute. These have been variably described as discrete clustered contractions in the small intestine\textsuperscript{139,140} or colonic migrating motor complexes\textsuperscript{133,141,142}. They appear to occur even in the empty mouse colon\textsuperscript{143}. 

176
There are relatively few studies of isolated preparations of human colon that address this question. In short isolated segments of normal colon regular large phasic slow contractions at minute intervals have been recorded which are insensitive to neural blockade (thus appear to be myogenic). Interestingly the authors of that work found that these myogenic slow contractions could be triggered and reset by intrinsic neural inputs, indicating the modulating role of neural inputs on myogenic activity. Also of relevance is the observation that in isolated long segments of human colon studied ex vivo, similar minute pattern of phasic contractions was recorded over long distances resembling the long single propagating motor pattern observed in some of our children. While this long-single motor pattern is present in healthy adults and adults with slow transit constipation, it only occurs in low numbers. This motor pattern becomes apparent when whole sections of human colon are studied in an organ bath, we therefore hypothesize that this motor pattern is normally suppressed in vivo. The most likely explanation for this is that the motor pattern is subject to ongoing enteric inhibitory inputs. Therefore abnormally decreased extrinsic neural activity may see these motor patterns revealed and this may explain their increased presence in a proportion of these children. Specific experiments need to be planned to test this hypothesis, which may have important consequences for clinical diagnosis, treatment and management.

Potential limitations and criticism of the study design and interpretation of data
There are some obvious limitations that need to be taken into account when interpreting these data. First, we have compared the motor patterns in constipated children to those recorded in healthy adults. In an ideal world our comparative data would come from healthy children. However, currently that is not ethically possible and it is unlikely to ever be so with this technique. Therefore, as we have done before, we have to use the next best option, healthy adults. While it could be argued that the numbers of the identified motor patterns may differ between healthy adults and healthy children, it is unlikely to explain the differences observed in this study. We have chosen to compare our pediatric data with the only available adult studies utilizing high-resolution colonic manometry while defining the four main motor patterns (HAPS, cyclic, short single and long single) that were previously defined.

Another limitation of our study is that in the pediatric patients different protocols were used to determine colonic transit time. In addition, in some of these severely constipated children parents did not permit the measurement of colonic transit if the procedure required their child to stop their constipation.
medication, such was their fear of deterioration of symptoms. Indeed laxatives were taken by some of those children that underwent the transit study. Consequently we were not able to categorize all patients as either slow transit constipation or outlet obstruction. The results however, have shown that the observed colonic motor abnormalities were similar between the studied children, indicating that while there are differences in colonic transit time, the colonic anomalies were consistent. In addition, the impaired postprandial response found in adult slow transit constipation patients was also observed in the studied pediatric patients, suggesting that these children show similarities with the adult patients.

Another potential criticism is the fact that the data in children were recorded with a water-perfused catheter, while in adults a fiber-optic manometry catheter was used. The recording fidelity of both systems is likely to differ and there may well be differences in the amplitude of the pressure events recorded. However, water perfused catheters detected the long single motor patterns in children. Since the characteristics of the pressure events that make up these motor patterns do not differ from those that make up the cyclic motor pattern it is unlikely the catheter could record one without the other. In addition non-propagating pressure events were recorded in every child. The failed meal response in children was also observed in adults with constipation, therefore either both manometric systems are incapable of recording the motor patterns in the patients or the differences were caused by the underlining pathology. Finally, a previous study has shown that motor patterns detected by water-perfused and solid-state manometry are comparable\cite{147}. While that study, used a very different protocol to ours, recording motor patterns simultaneously with both catheters in the same subject at the same time, these data indicate that water perfused manometry is capable of detecting both low and high amplitude contractile activity. The perfusate could be responsible for the increase in the long single propagating contractions, however we are finding the same motor pattern in children recorded with solid state catheters in USA (data unpublished).

It is also possible that the different sensor spacing (1.5 cm in water perfused versus 1 cm in fiber-optic) resulted in fewer propagating motor patterns being detected with the water-perfused catheter. While we have previously shown that the number of propagating motor patterns identified is dependent upon the catheter sensor spacing\cite{60}, the apparent chaotic nature of pressure events recorded in adjacent channels in the colon of these children (see figure 3A) indicates that a slight decrease in the sensor spacing would be unlikely to transform these into organized motor patterns.

Another difference between adult and pediatric protocols involved the meal
that study subjects received. Adult patients received a set meal, whereas children were given a meal of free choice, which had an age dependent calorie load. The decision of a free choice meal for the children was made to ensure that they ate a meal. While there have been a number of studies that demonstrate the effects of different meals upon the colon\textsuperscript{148,149} it is important to note that in all instances the colon responds to a meal. Indeed a study by Price et al\textsuperscript{150} demonstrated that meal containing 70% fat or carbohydrate or protein all resulted in a gastrocolonic response and none of the different compositions had any effect upon ileo-colonic transit. In our own data the meal response in healthy adults occurred within a minute of starting the meal (see fig 2 in \textsuperscript{150}). Thus it is clear that it is not required for adults to finish the entire 700kcal meal for this response to start. Therefore the absence of the meal response in the constipated children cannot be explained by the difference in meals.

In conclusion, as seen in adults with slow transit constipation, high-resolution colonic manometry enables quantification of motor pattern abnormalities in children with chronic intractable constipation. Results show that these children lack a physiological increase of retrograde cyclic propagating motor patterns after the meal and have significantly more long single propagating motor patterns prior to a meal. Spontaneous postprandial HAPS were rarely seen in children, however they could be induced by bisacodyl in the majority. Future research should focus on all identified colonic motor patterns, rather than on HAPS alone.
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181


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