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Lactulose Breath Test Gas Production in Childhood IBS is Associated with Intestinal Transit and Bowel Movement Frequency

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Abstract

Background—In adults with irritable bowel syndrome (IBS), bacterial gas production (colonic fermentation) is related to both symptom generation and intestinal transit. Whether gas production affects symptom generation, psychosocial distress, or intestinal transit in childhood IBS is unknown.

Methods—Children (ages 7-17 years) with pediatric Rome III IBS completed validated psychosocial questionnaires and a 2-week daily diary capturing pain and stooling characteristics. Stool form determined IBS subtype. Subjects then completed a 3-hour lactulose breath test for measurement of total breath hydrogen and methane production. Carmine red was used to determine whole intestinal transit time.

Results—87 children (mean age 13 ± 2.6 (SD) years) were enrolled, of whom 50 (57.5%) were female. All children produced hydrogen and 51 (58.6%) produced methane. Hydrogen and methane production did not correlate with either abdominal pain frequency/severity or psychosocial distress. Hydrogen and methane production did not differ significantly by IBS subtype. Methane production correlated positively with whole intestinal transit time ($r=0.31$, $P<0.005$) and inversely with bowel movement frequency ($r= -0.245$, $P<0.05$). Methane production (threshold 3 ppm) as a marker for identifying IBS-C had a sensitivity of 60% and specificity of 42.9%.

Conclusions—Lactulose breath test total methane production may serve as a biomarker of whole intestinal transit time and bowel movement frequency in children with IBS. However, in children with IBS, lactulose breath test hydrogen and methane production did not correlate with either abdominal pain, IBS subtype, or psychosocial distress.

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INTRODUCTION

Childhood abdominal-pain related functional gastrointestinal disorders (AP-FGID) affect up to 20% of school aged children and cause significant morbidity (1). AP-FGID are the reason for a significant number of primary and tertiary care consultations (1). Up to 65% of children with AP-FGID have irritable bowel syndrome (IBS) (2). Children with IBS can be further subtyped based on their predominant stool form: IBS with diarrhea (IBS-D); IBS mixed type (IBS-M); IBS un-subtyped (IBS-U), and IBS with constipation (IBS-C) (3). The etiology of childhood IBS is multifactorial. These factors include: carbohydrate intolerance, chronic inflammation, psychosocial distress, gut microbial dysbiosis, visceral hypersensitivity, and colonic fermentation (4-6).

As measured by gas production in adults with IBS, overall colonic carbohydrate fermentation is increased (7). Gas production increases when both adults and children with IBS consume fermentable oligosaccharides disaccharides monosaccharides and polyols (FODMAP) such as fructose (8, 9). The gas production from carbohydrate fermentation leads to luminal distention; and this in turn may generate gastrointestinal (GI) symptoms (10). In addition fructose malabsorption, which leads to increased fermentation, has been associated with increased psychosocial distress (depression) in adults with IBS (11).

Colonic fermentation is modified by both age and the composition of the colonic microbiota (12, 13). Compared to healthy adults, healthy children have a unique gut microbial composition (14); furthermore, the gut microbiome composition in children with IBS vs. healthy children differs (6). The manner in which both these childhood specific and IBS specific differences in colonic microbiome composition affect colonic fermentation in children with IBS is unknown.

An index of microbial colonic fermentation can be determined through hydrogen and methane breath testing following ingestion of a nonabsorbable carbohydrate such as lactulose (15). Lactulose enters the colon essentially intact where it is used as a fermentable substrate by colonic bacteria resulting in hydrogen and methane production (16). In adults, lactulose breath testing in those who are healthy versus those with functional gastrointestinal disorders has identified different breath gas profiles (17). In adults, IBS investigators have found mixed results when correlating these gas production profiles following a lactulose challenge to GI symptoms, psychosocial distress (e.g., depression), stool form, and IBS subtype (18, 19). To date, these potential relationships have not been investigated in childhood IBS. Therefore, we undertook a prospective evaluation to determine in children with IBS the potential relationship of hydrogen and methane gas production following the lactulose breath test to several factors including: abdominal pain, psychosocial distress, bowel habits, IBS subtype and intestinal transit.

METHODS

Recruitment & Data Collection

Participants (ages 7-17 years) were enrolled who were part of a larger randomized treatment trial for children with Rome III IBS. Only baseline data obtained prior to any randomization

or intervention were used. Participants were recruited from both primary and tertiary care clinics within a large academically-affiliated pediatric health care network. Potential participants were identified through chart review for ICD-9 codes 789.0 (abdominal pain) or 564.1 (irritable bowel syndrome). Parents of potential participants were contacted by mail and if interested were screened by phone for inclusion and exclusion criteria.

All participants met pediatric Rome III IBS criteria (1). Children were excluded if screening identified any of the following: an organic GI illness, a chronic health condition requiring daily medication or specialty follow-up care, decreased growth velocity, GI blood loss, unexplained fever, chronic vomiting, weight loss ≥5% within a 3-month period, current use of anti-inflammatory medications, or previous symptomatic relief from use of a GI medication (e.g., proton pump inhibitor). Additional exclusion criteria included either lack of fluency in English (as the administered psychological questionnaires are only available in English) or a developmental disability. The study was approved by the Baylor College of Medicine Institutional Review Board. Both parent consent and child assent were obtained.

Pain & Stool Diary

During a home visit, parents and children were instructed on the completion of a daily pain and stool diary. Parents were asked to remind children to complete the diaries daily; children made independent ratings. Children rated abdominal pain for three intervals each day (morning, midday/afternoon, and evening/nighttime) using a validated 0-10 numerical scale. This scale was anchored with the phrases “no pain at all” and “the worst pain you can imagine” (20). Children also reported the degree of activity interference due to pain using a 4-point scale. Activity interference ranged from no interference to “could not participate because of pain.” Children both recorded the time of each stool and using the Bristol Stool Form Scale rated stool consistency (21). Using stool frequency and stool consistency data, children were further subtyped into IBS-C, IBS-D, IBS-U, or IBS-M using Rome III criteria (3).

Psychosocial Measures

All subjects completed psychosocial measures at the time of the home visit. These included: the Children's Somatization Index; the Functional Disability Inventory; and the Behavioral Assessment for Children, Second Edition.

The Children's Somatization Inventory rates 35 items. Each item lists a symptom (e.g. headache). The child rates the degree to which they are “bothered by each symptom” over the preceding two weeks using a 5-point Likert scale (0=”not at all” to 4=”a whole lot”).(22) Children's Somatization Inventory total scores range between 0 and 140; increasing scores indicate greater levels of somatization.

The Behavioral Assessment System for Children, Second Edition (BASC-2) assesses behavior and emotional dimensions of children and has extensive support for reliability, content and construct validity.(23) The child self-report questionnaires are available for children ages 6 to 21 years. The child self-report scales are derived from established norms with a mean score of 50 and a standard deviation of 10. We used the BASC-2 T-scores for Anxiety and Depression.

The Functional Disability Inventory is a 15-item questionnaire. This measures the degree to which children have self-perceived difficulty in physical and psychosocial functioning (24). The Functional Disability Inventory total scores range from 0-60; higher scores reflect higher levels of perceived disability.

Lactulose Breath Test

During the home visit subjects were instructed on the proper usage of a breath test collection kit (QunTron® Instrument Co., Milwaukee, WI, USA). Following a low carbohydrate dinner the night before and an overnight fast, children completed a 3-hr lactulose breath test. Baseline hydrogen (ppm) and methane (ppm) concentrations were captured during exhalation. Following this, subjects ingested 10 g of lactulose in 250 mL of water. Subjects then captured an exhaled breath every 15 minutes thereafter for a total of 180 minutes. During the breath testing subjects were not allowed to eat other foods or exercise. The breath samples were analyzed using a QuinTron® model SC gas chromatograph. Subjects who excreted ≥ 3 ppm of methane in at least one of the breath samples were characterized as methane producers (18). Total hydrogen and methane gas production was calculated as the area under the curve using the trapezoidal method. The area under the curve units are expressed as parts per million * minute (ppm * min).

Carmine Red Test

Children opened a capsule containing carmine red and mixed this into the lactulose breath test solution. The time of solution ingestion was recorded. Children then collected their next four bowel movements. These bowel movements were sent back to the investigators for visualization. Subjects noted the day and time for each bowel movement sample.

Whole intestinal transit time was calculated as the time from ingestion to the first stool sample demonstrating reddish coloring. For those subjects without reddish coloring in any of the stools submitted whole intestinal transit time was calculated as the time from ingestion of the carmine red to the last (fourth) provided stool sample in order to objectively capture a minimum threshold for whole intestinal transit for the subject.

Statistical Analyses

IBM SPSS Statistics, Version 22 (Armonk, NY) was used for statistical analysis. Several factors were calculated for each subject over the two week period including: mean pain rating, defined as the mean severity of all the pain episodes; maximum pain rating, defined as the highest severity score of any of the pain episodes; and pain frequency.

Spearman correlation was calculated between hydrogen and methane production and pain parameters, psychosocial distress scores, bowel movement frequency, and whole intestinal transit time. Wilcoxon (non-parametric) testing compared IBS-subtypes and hydrogen and methane production. Unless otherwise noted, data are presented as mean ± standard deviation and P-values less than 0.05 are considered significant.

RESULTS

Characteristics of subjects

Eighty-seven children with IBS completed the lactulose breath test; of which 50 (57.5%) were female. Mean age was 13.4 ± 2.6 (SD) years. Race/ethnicity distribution was as follows: 51 (58.6%) Caucasian, 10 (11.5%) Black, 22 (25.3%) Hispanic, 2(2.3%) Asian, and 2 (2.3%) Mixed. Seventy (80.5%) had a PPO/HMO for insurance coverage, 14 (16.1%) Medicaid/CHIP, and 1 (1.1%) were self-pay. IBS subtypes were as follows: 45 (51.7%) IBS-C, 35 (40.2%) IBS-U, 5 (5.7%) IBS-D and 2 (2.3%) IBS-M.

Gas production

All subjects produced hydrogen. Fifty-one (58.6%) of subjects produced methane at a threshold of ≥ 3 ppm. Mean hydrogen production in all subjects was 4605 ± 3389 ppm*hr. Mean methane production in all subjects was 1051.55 ± 2350 ppm*hr.

Correlation of Abdominal Pain Characteristics to Gas Production

We did not identify significant relationships between hydrogen or methane total production and pain severity, pain frequency, or pain interference of activities (Table 1).

Correlation of Psychosocial Distress to Gas Production

All children had BASC-2 validity index scores that were within the normal range for both response pattern and consistency (23). We did not identify significant relationships between either hydrogen or methane production to anxiety, depression, functional disability, or somatization (Table 1).

Correlation of Bowel Movement Frequency and Intestinal Transit to Gas Production

Mean whole intestinal transit time in the population was 2609 ± 2440 minutes. There was a significant positive correlation between whole intestinal transit time and methane production ($r=0.31$, $P<0.005$). Methane production was negatively correlated with the number of daily bowel movements ($r=-0.25$, $P<0.05$). In contrast, we did not find a statistically significant relationship between hydrogen production and either bowel movement frequency or intestinal transit time.

Correlation of IBS Subtype to Gas Production

We did not identify differences by IBS subtype in hydrogen or methane production (Table 2). Methane production was found in many of those with IBS-C and IBS-U; but methane was not specific to these two groups (Table 3). The sensitivity and specificity of methane as a marker for IBS-C identification varies by the threshold used with a sensitivity of; sensitivity of 60% and specificity of 42.9% at a 3 ppm threshold; and a sensitivity of 42.2% and specificity of 54.8% at a 5 ppm threshold.

DISCUSSION

In this prospective cohort evaluation we found that lactulose breath test methane production in children with IBS correlates positively with whole intestinal transit time and negatively

with bowel movement frequency. However, we found that lactulose breath test total hydrogen and methane production in children with IBS was not related to abdominal pain characteristics, psychosocial distress, or IBS subtype.

To our knowledge our findings related to methane and intestinal transit in children with IBS is novel; this may deserve further investigation given the search for clinically applicable childhood IBS biomarkers. Methane as a primary culprit for actively slowing colonic transit is supported by *in vivo* animal studies (25); however, the mechanism has not been fully established (26). Elevated methane production has previously been found in childhood constipation related disorders. Higher methane production was reported in children with retentive fecal incontinence (27). Using radio-opaque markers in children with chronic constipation Soares et al. found methane production correlated with colonic transit time (28). Decreases in methane production occurred following successful treatment of the underlying childhood constipation condition (28, 29). Extending the results of this study and borrowing from the experience of these other studies, clinicians may be able to use methane production from the lactulose breath test as a biomarker in children with IBS both to determine the presence of a prolonged intestinal transit as well as to assess the efficacy of intestinal transit focused therapies such as laxatives.

Despite our findings with respect to intestinal transit we did not identify a significant difference in methane production relative to childhood IBS subtypes. Higher methane production was seen in those with IBS-C; however, this was not significantly different from that seen in other subtypes, particularly IBS-U. It is important to note that Rome III subtypes are determined by stool form as rated by the Bristol Stool Form Scale and are not completely predicated on transit time (30). The correlation of whole intestinal transit and the Bristol Stool Form Scale was validated at $r = -0.54$ (21); thus, suggesting a good but not perfect correlation. Future studies enrolling an even larger cohort of children with IBS may be able to identify further differences in gas production by subtype, perhaps by using stool scales which have been validated for use in children (31, 32).

Methane production correlation to adult IBS symptoms has been investigated with mixed results. Chaterjee et al. reported that methane production correlated with decreased bowel movement frequency (33). However, Lee et al. did not find a relationship between methane production and adult IBS constipation severity (19). Hwang et al. reported (using both Rome I criteria and a threshold of 5 ppm to define a methane producer) that methane production was significantly more common in those with IBS-C (18). However, a recent study demonstrated that a 5 ppm breath testing threshold to define a methane producer was not an accurate marker of colonic methane production (34). In contrast, Lee et al. (using both Rome III criteria and a threshold of 1 ppm to define a methane producer) did not find a difference in the proportion of methane producers by IBS subtype (19). Given the different approaches in the literature, and a desire to begin at a threshold above the gas chromatograph's accuracy (±2 ppm), we chose to evaluate different cut-offs (including 3, and 5 ppm of methane). Using these different thresholds we did not find any marked improvements in sensitivity or specificity with identification of a child with the IBS-C subtype. Future studies assessing gas production directly from the colon in children with IBS may help shed further light into the relationship between gas production and IBS symptoms.

Carbohydrate fermentation as an inducer of gastrointestinal symptoms (particularly in the context of dietary interventions) has received significant attention in recent adult and pediatric IBS studies (9, 35). The lack of a correlation with IBS abdominal pain symptoms or psychosocial distress with lactulose breath test gas production suggests either that a lactulose challenge alone may not be a good comprehensive carbohydrate fermentation surrogate marker (and is unlikely to be a good predictor of response to interventions such as the low FODMAP diet) or that symptoms related to carbohydrate fermentation may be related to other factors beyond gas production. Le Neve et al. have recently combined both a nutrient drink and high dose lactulose (25 g) over 4 hours and found a strong correlation of gas hydrogen and methane gas production to adult IBS symptoms and psychosocial distress (36). The diagnostic utility of other nutrient challenges with or without other carbohydrates or different test carbohydrate doses in children with IBS needs to be determined. In addition, the mechanism by which nutrients combined with lactulose may affect GI symptoms and psychosocial distress remains to be elucidated as Le Neve et al. did not identify a correlation with fecal microbiota composition (36).

Other factors beyond gas production may influence the pathogenesis of symptoms in children with IBS following carbohydrate ingestion, including visceral hyperalgesia. Yang et al. found that adults with IBS-D with lactose malabsorption who developed symptoms (in comparison to those who did not) had higher visceral hyperalgesia (37). Therefore both visceral hyperalgesia and gas production resulting from malabsorption may be required for symptom generation. Alternatively, we have previously demonstrated that children with IBS who responded to a dietary intervention (in comparison to those who did not respond to the same intervention) had different fecal microbiome and metabolite compositions (9, 38). Whether other bacterial metabolites apart from gas correlate with symptoms in childhood IBS remains to be determined.

Limitations of this study include the sample size, though to our knowledge this is the largest prospective study of children with IBS undergoing lactulose breath testing. Another limitation includes the lack of carmine red in the stools for some of the subjects. This only allowed for the calculation of a minimum threshold for whole intestinal transit in these subjects. Future studies evaluating whole intestinal transit time in this population may consider collecting more stools, asking participants to photograph stools, or use another whole intestinal transit time measure. In addition, the study was conducted at one tertiary care center. Further evaluations at other centers will lend greater generalizability to the results. Finally, the lactulose breath test has been used by other investigators to diagnose small bowel bacterial overgrowth (39). However, more recent data suggest that the rise in hydrogen following consumption of lactulose actually reflects orocecal transit time (17, 40). Future studies may consider evaluating for small bowel bacterial overgrowth once a noninvasive gold standard is available.

In summary, we found that lactulose breath test total (area under the curve) methane production in children with IBS correlates with both whole intestinal transit and decreased bowel movement frequency. However, lactulose breath test hydrogen and methane production in children with IBS was not related to abdominal pain characteristics, psychosocial distress, or IBS subtype.

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What is Known

- In adults with irritable bowel syndrome (IBS), bacterial gas production (colonic fermentation) is related to both symptom generation and intestinal transit.
- In adults with IBS, hydrogen and methane gas production during a lactulose breath test has been associated with gastrointestinal symptom severity, psychosocial distress, and IBS subtype.
- Children have a different gut microbiome composition as compared to adults

What is New

- Lactulose breath test methane production in children with IBS correlates with both whole intestinal transit time and decreased bowel movement frequency
- Lactulose breath test hydrogen and methane production in children with IBS is not related to abdominal pain characteristics, psychosocial distress, or IBS subtype

Table 1

Relationship of Lactulose Breath Test Hydrogen and Methane Production to Abdominal Pain Characteristics and Psychosocial Distress in Children with IBS (n=87). None of the relationships were statistically significant.

Parameter	Mean ± SD	Hydrogen r-Value	Methane r-Value
Abdominal pain episodes/ 2 weeks	15.9 ± 10.9	0.12	−0.1
Mean pain severity (0-10)	3.3 ± 1.1	−0.16	−0.13
Anxiety*	53.9 ± 11.8	−0.1	−0.09
Depression*	48.6 ± 10.0	0.03	−0.01
Child Somatization Inventory Score	29.4 ± 18.3	0.06	−0.14
Functional Disability Inventor Score	13.7 ± 10.3	0.13	−0.2

*Behavioral Assessment for Children, Second Edition T-score

Table 2

Values (Area Under the Curve) by Childhood Irritable Bowel Syndrome Subtype for Lactulose Breath Test Hydrogen and Methane Production.

IBS Subtype	Hydrogen (ppm*min)	Methane (ppm*min)
IBS-C (n=45)	4391 ± 3482	1666 ± 3093
IBS-U (n=35)	4907 ± 3498 *	456 ± 730 **
IBS-D (n=5)	4245 ± 2039	26 ± 40
IBS-M (n=2)	5063 ± 3903	199 ± 281

Mean ± SD

There were no statistically significant differences between the Irritable Bowel Syndrome subtypes. IBS-C= IBS with constipation; IBS-U= IBS unsubtyped; IBS-D= IBS with diarrhea; IBS-M= IBS with mixed subtype; parts per million * minute = ppm*min

* P-value hydrogen production comparison for IBS-C vs. IBS-U: P=0.44

** P-value methane production comparison for IBS-C vs. IBS-U: P=0.41

Table 3

Proportion of Lactulose Breath Test Methane Producers Using Two Different Thresholds in Children with Irritable Bowel Syndrome

IBS Subtype	Methane Production (≥3 ppm threshold)	Methane Production (≥ 5 ppm threshold)
IBS-Constipation (n=45)	27 (60%)	19 (42.2%)
IBS-Unsubtyped (n=35)	23 (65.7%)	18 (51.4%)
IBS-Diarrhea (n=5)	0	0
IBS-Mixed Type (n=2)	1 (50%)	1 (50%)

Methane production was defined as an individual producing any amount of breath methane following lactulose ingestion greater than or equal to the defined threshold. There were no statistically significant differences in the proportion of methane producers between irritable bowel syndrome subtypes.