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Autonomic Nervous System Function in Young Children With Functional Abdominal Pain or Irritable Bowel Syndrome

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Abstract

Adults with irritable bowel syndrome (IBS) have been reported to have alterations in autonomic nervous system function as measured by vagal activity via heart rate variability. Whether the same is true for children is unknown. We compared young children 7 to 10 years of age with functional abdominal pain (FAP) or IBS to healthy children (HC) and explored the relationship of vagal activity and sympathovagal balance to psychological distress and stool type. Children completed questionnaires, kept a 2-week pain/stool diary, and wore a 24-hour Holter monitor to assess vagal activity. Group comparisons on vagal activity were controlled for age and body mass index. Indicators of vagal activity and sympathovagal balance did not differ between FAP/IBS children (70 girls, 30 boys) and HC (44 girls, 18 boys). Psychological distress measures were generally higher in FAP/IBS than HC, primarily in girls. Exploratory analyses suggest a potential negative correlation between vagal activity and psychological distress in FAP/IBS girls but not boys. In contrast to reports in women, no differences were found in vagal activity between FAP/IBS and HC. Preliminary findings suggest that in girls with FAP/IBS there is an inverse relationship between vagal activity and psychological distress.

Perspective—The results from this study suggest a possible relationship between emotional state and vagal activity in prepubertal girls (but not boys) with FAP/IBS. Age and/or duration of symptoms may explain our contrasting findings versus adults with IBS.

Keywords

Children; functional abdominal pain; heart rate variability; irritable bowel syndrome

Recurrent abdominal pain (RAP) occurs frequently in school age children.^{4,23,26} Saps and Sztainberg²⁶ found that 18% of 209 school children experienced abdominal pain over 12 consecutive weeks. The original definition of RAP was intermittent abdominal pain in

children between the ages of 4 and 16 years that persists more than 3 months and affects normal activity.¹ The Pediatric Rome Committee now has subdivided RAP into the terms irritable bowel syndrome (IBS) and functional abdominal pain (FAP) based on whether the pain is associated or not with changes in stool character.²⁵ FAP/IBS in children share many similarities to FAP or IBS in adults and may be precursors to these disorders in adults.^{12,37}

A number of potential mechanisms may underlie the symptoms of FAP and IBS in children. One possibility is that abnormalities of the autonomic nervous system (ANS) could lead to pain and bowel problems. Vagal activity as measured by heart rate variability is used commonly as an index of parasympathetic ANS function and is related to age, gender, and heart rate.²² Low vagal activity can lead to decreased bowel contractions, reduced motility, and constipation, while high vagal activity can lead to increased contractions and diarrhea.¹⁹ Studies in adults have demonstrated that IBS women with constipation and severe pain have lower vagal activity than controls.³ In children, interpretation of studies of vagal activity in FAP/IBS compared with controls is hampered by study design issues and modest sample sizes.^{21,24}

In adults with IBS, there is also an inverse relationship between psychological distress and vagal activity.¹³ Whether the same is true for children is unclear. This is an important question given that children with RAP have higher levels of anxiety, depressive and somatic symptoms, and lower functional ability compared to well children.^{5,35,36}

As alluded to above, women with IBS constipation have lower vagal activity compared with those with IBS diarrhea or IBS mixed types.¹⁴ To our knowledge, potential vagal activity/stooling pattern relationships have not been investigated in children with FAP/IBS.

As might be anticipated from the above studies, stooling pattern may relate to the interaction of both vagal activity and psychological state. Indeed, Emmanuel et al⁶ have shown in adults with IBS that there is a relationship between psychological distress (eg, depression, anxiety), decreased vagal activity as reflected by heart rate as well as rectal mucosal blood flow measurements, and stooling pattern (constipation). Whether the same is true for children is unclear.

Thus, we hypothesized that ANS function as measured by vagal activity differs in young children with FAP/IBS compared with healthy comparison children (HC). We also hypothesized that there would be relationships between vagal activity and psychological distress and pain and stool characteristics in young girls and boys separately, given that vagal activity can differ by age and gender.²²

Methods

Design and Sample

An observational design was used to compare children, 7 to 10 years of age, who met the criteria for FAP or IBS to a group of HC without abdominal complaints. Both FAP/IBS and HC children were recruited from the Texas Children's Hospital health care network that provides primary and tertiary care throughout the Houston metropolitan area. To identify potential children who met the criteria for FAP/IBS, a search was conducted based on ICD codes for abdominal pain (789) and IBS (564.1). HC were screened based on at least 1 healthy code/visit to the pediatrician within the past year and were matched for age and sex to the FAP/IBS group. The charts were reviewed to establish potential eligibility. Once potential participants were identified, a letter inviting the family to participate was sent to potential subjects' parents by their respective physician within a month. Interested parents

and children were given details about the study and further screened over the telephone for eligibility.

Both children with FAP and IBS met Pediatric Rome II criteria with the addition that their pain severity was $\geq 3/10$ as recommended by Rasquin et al²⁵ and von Baeyer.³² Children in the HC had to be free from current stomach pain in the last year (except for acute viral illnesses) and had to meet the same exclusion criteria as the FAP/IBS children. Exclusion criteria included an organic (nonfunctional) gastrointestinal (GI) disorder, other significant chronic health conditions requiring daily medication (eg, diabetes) and/or specialty care follow-up (eg, congenital heart disease). Children with mild chronic illnesses such as asthma were not excluded. Other exclusion criteria included an abnormal physical examination, decreased growth velocity, menstruation, GI blood loss, unexplained fever, vomiting, chronic severe diarrhea, unexplained weight loss within a 3-month period, current use of anti-inflammatory (eg, ibuprofen) or GI (eg, proton pump inhibitors) medications, and for FAP/IBS children, previous use of GI medications that provided complete relief of GI symptoms as by definition, these children did not have FAP or IBS.

Procedures

This study was approved by the Human Subjects' Institutional Review Board. The research coordinators visited the subject's house and obtained informed written parental consent and child assent. Children were measured for height and weight. The psychological questionnaires were administered to the children by the research coordinators. Verbal and written directions then were given to the child and parent on how to complete the pain and stool diary. Parents were allowed to assist the child with the stooling diary to ensure that the record was kept and assist with comparison to the pictures on the stooling diary. The children were assessed for medication use. If they were taking an antispasmodic (eg, hyoscyamine) they were asked to not use it the evening and night when the Holter recording was done. At the end of the visit the staff applied 7 electrodes for the 24-hour Holter recording of vagal activity. The next day the recorder was removed.

Vagal Activity, Sympathovagal Balance and General Measures

An ambulatory ECG 3-channel compact digital Holter was used to record beat-to-beat intervals over a 24-hour period (Cardiac Science/Burdick Inc., Deer-field, WI) and processed using Burdick Vision Premier analysis software by a trained technician. A standard set of spectral (frequency domain) measures were used. The spectral measures are based on a discrete Fourier transform (DFT/FFT) spectral analysis algorithm applied to successive 5-minute blocks of normal sinus R-R intervals. The measures were summarized for 24 hours, day (1 PM to 5 PM), and night (2 AM to 6 AM) phases.

Heart rate variability measures reflecting central parasympathetic (vagal) activity included the spectral measure high frequency (HF). The power (variance) in the HF band was estimated by summation of the heart rate variability spectrum between frequencies of $f = .15$ and $f = .40$ Hz.^{10,15,22}

The general spectral measure low frequency (LF) (sympathovagal) was computed as the power in the spectrum between frequencies of $f = .016$ and $f = .15$ Hz.^{10,15,22} Vagal activity measures were then computed as the ratio of spectral low frequency/high frequency (square root of LF/HF).^{10,15,22}

Psychological Distress

The State-Trait Anxiety Scale for Children (STAIC) was used to assess trait and state anxiety in children using 20 items (40 items total) rated on a 3-point scale: 1 (hardly ever), 2

(sometimes), 3 (often).²⁹ The scale was validated initially on children 9 to 12 years of age but the authors state that the STAIC can be used with younger children with average reading levels. The scale was read to children under 9 years of age. Internal consistency for children 7 to 8 years was $\alpha = .650$ (State) and $\alpha = .744$ (Trait), and for children 9 to 10, $\alpha = .886$ (State) and $\alpha = .858$ (Trait). A sum score was used and a higher score reflects greater anxiety.

The Children's Depression Inventory (CDI) measured symptoms of depression.^{16,17} Each of the 27 items are rated 0 (eg, I like myself), 1 (eg, I do not like myself), or 2 (eg, I hate myself). The CDI has good internal consistency ($\alpha = .84$ to $.89$), adequate test-retest reliability, and discriminant validity.²⁷ The internal consistency for this sample was $\alpha = .84$. A cutoff score of 16 has a total predictive value of 86% when screening to detect depressive disorders in youths and differentiates depressive disorders from anxiety and disruptive disorders.³⁰ The sum score was used and higher scores reflect more severe symptoms.

The Children's Somatization Inventory (CSI) indexed somatic complaints by the child and was developed from the DSM-III-R criteria for somatization and the Hopkins Symptom Checklist somatization factor.^{33,34} The scale has been used for children 6 to 18 years; the items were read to children as recommended. Children rated the extent to which they experienced 35 symptoms in the previous 2 weeks on a Likert scale from 0 (not at all) to 4 (a whole lot). Three-month test-retest reliability is $r = .50$ for well children and $r = .66$ for children with a chronic pain problem. The internal consistency for this sample was $\alpha = .95$. The items were summed with a higher score indicative of greater disability.

Pain and Stooling Diary

The children recorded pain episodes in the diary. The number of stomach pain episodes over the 2 weeks was calculated. In the daily pain diary, children rated their pain severity (intensity) on a 100-mm visual analogue scale at wake up, after lunch, and before bed for 2 weeks.²⁸ The anchors were 0 mm (no pain at all) and 100 mm (worst pain you can imagine). The daily ratings were determined by measuring the distance from the left end of the line to the child's "X" in mm. The number of pain episodes was calculated per week averaged over 2 weeks. The maximum pain recorded on the VAS for each day was noted and was used to calculate a mean maximum score for that week. Pain severity then was calculated as the mean of the 2 weekly scores. The child also rated how much the pain interfered with their activities on a scale from 0 (not at all) to 4 (could not participate because of pain).²⁸ Interference was calculated in the same way as pain severity; generating a mean maximum interference score for the week and then using the mean of the 2 weekly scores.

In the stool diary, children recorded the date and time that stools were passed. The consistency of bowel movements were rated by the child as 1 (watery), 2 (mushy), 3 (formed), or 4 (hard) based on pictures provided in the diary that were analogous to the Bristol Stool Form chart.¹⁸ If no stool was passed the child marked 5 (no bowel movement). Stool frequency was calculated as mean number of stools per week averaged over 2 weeks and percentage of days with no stools over 2 weeks. Stool consistency was summarized as the percent of stools that were watery or mushy, or formed (normal), or hard over 2 weeks.

Data Analysis

Data are presented as mean $\pm$ SD unless otherwise noted. Differences in descriptive characteristics were tested using a Fisher's Exact or Pearson Chi-square test (FAP/IBS versus HC) for categorical variables, and independent t-tests and nonparametric Mann-Whitney U tests (FAP/IBS versus HC) for continuous variables. Univariate analysis of

covariance (ANCOVA) was used to compare vagal activity by group (FAP/IBS versus HC), controlling for age and body mass index, and stratifying by child's gender.

For each psychological, pain, or stooling measure, linear regression analysis was used to evaluate the relationship of that predictor variable and group membership to each of the vagal activity. Each model included the predictor variable, a group indicator, and the group by predictor interaction. The focus was on the interaction term, since a significant interaction would indicate some relationship of group to vagal activity. Since some interactions were significant, results are presented as regression slope within each group, and the *P* value for the interaction (ie, the difference in slopes). For this exploratory aim a number of comparisons were done. Thus, we recognized the need for cautious interpretation of the results. Sample size was determined based on differences seen between IBS and Controls in the adult studies of heart rate variability.^{3,11,13} Sample sizes chosen intentionally were made more robust than in the adult or previous pediatric studies to reduce the risk of a type 2 error.

Results

A STROBE flow diagram for screening, recruitment, and study participants is given in Fig 1.³¹ Demographic data are provided in Table 1. Analyses were done initially to determine if the 30 children with IBS differed from the 70 children with FAP on the key study variables. No differences were found so the groups were combined.

The analyses were stratified by gender in part, due to a strong statistical main effect on heart rate. Boys had lower heart rates than the girls, especially when measured at night independent of whether they had a FAP/IBS diagnosis (70.3 ± 6.8 versus 74.4 ± 8.1 , respectively; *P* = .001).

Table 2 shows comparisons of vagal activity measures between FAP/IBS and HC, for boys and girls separately. None of the 3 vagal activity measures, whether 24 hour, day, or night showed any evidence of FAP/IBS differing from HC.

Trait anxiety, depression, and somatization scores were significantly higher in girls with FAP/IBS versus HC girls (Table 2). Nineteen (27%) of the girls with FAP/IBS had depressive symptoms (CDI score of 16 or greater) versus only 2 (5%) of HC girls (Odds Ratio 7.67, 95% Confidence Interval, 1.7–34.8; *P* = .003). Most of these variables showed similar trends among boys but with less significant *P* values, partially explicable by the smaller sample of boys (Table 2). Only 3 (10%) of boys with FAP/IBS versus 1 (6%) of HC boys had a CDI score of 16 or greater (Table 2).

Pain episodes, pain severity, and interference with activity were more frequent or higher in the FAP/IBS group versus the HC group both for girls and boys (Table 2). Stool frequency and consistency did not differ within the girl or boy groups.

Among all the regression analyses done testing for interactions, the ones that found a significant group by predictor interaction were those involving nocturnal vagal activity measures as outcomes, and psychological distress measures as predictors (Table 3). For example, the first row shows that among girls with FAP/IBS there was a significant negative relationship of trait anxiety to vagal activity (*P* = .001) while among HC girls the relationship was not significant (*P* = .146). The interaction *P* value of .002 indicates that the 2 slopes are significantly different from each other. Fig 2 illustrates this interaction. In girls with FAP/IBS, as anxiety increased there was a corresponding decrease in vagal activity that was not present in boys with FAP/IBS in or HC girls or boys. Somatization also showed significant interaction *P* values for girls (Table 3) but none for boys (data not shown). For

sympathovagal balance, 2 measures showed significant interactions (trait anxiety and depression) for girls (Table 3) but none for boys (data not shown).

Discussion

The results from our study indicate that as a group, young children with FAP/IBS do not differ from HC in vagal or sympathovagal balance as measured by indicators of heart rate variability. There is limited information on ANS activity as measured by vagal activity in children with RAP. Olafsdottir et al²¹ measured vagal activity in 25 children with RAP and 23 Controls, ages 7 to 15 years using ECG recordings for 2 minutes. To assess psychosocial factors they used the Personality Inventory for Children.²¹ However, they did not relate the vagal activity to the Personality Inventory results.²¹ They also found no difference in vagal activity between groups. More recently, Puzanovova et al²⁴ compared 45 children with RAP and 22 well children ages 9 to 16 on their heart rate and vagal activity response to performance expectation (success or failure) compared to well children. During the success task (predicting a sequence of shapes and colors) children with RAP experienced a significant rise in vagal activity and sympathovagal balance compared to no change in the well children. Our results are difficult to compare to those of Olafsdottir et al²⁴ and Puzanovova et al.²⁴ First, they included both young children and teenagers in their samples and it is known there are maturational changes in vagal activity within the age span they studied.⁸ Second, results from short timeframe recordings may differ from ECG recordings made over a 24-hour period.⁷

Although women with IBS as a group do not differ from healthy women in regard to vagal activity, IBS women with severe abdominal pain and constipation-predominant symptoms had a significantly lower LnHF and higher sqrt LF:HF ratio than those with severe pain and a diarrhea-predominant phenotype.^{3,14} Unfortunately, there are no pediatric criteria for defining predominant bowel patterns in children with IBS (eg, diarrhea-predominant). Thus, we could only evaluate stool frequency and stool character for the groups as a whole in comparison to vagal activity. No significant relationships were seen between FAP/IBS children's stooling pattern or pain frequency or severity with vagal activity measures.

Because of earlier findings that anxiety and depression may be associated with lower parasympathetic activity in women with IBS as well as healthy women, we carried out exploratory analyses to evaluate psychological measures and vagal activity (Table 3).¹³ Similar to women with IBS, our results showed that girls with FAP/IBS who scored high on psychological symptoms were more likely to have lower vagal activity and in some cases higher sympathovagal balance. In contrast, similar findings were noted for healthy women in that study but not for healthy children in our study (Table 3).¹³ Our findings in FAP/IBS girls and those reported for adult IBS women support the neuroenteric dysregulation model of IBS that suggests there is a relationship between emotional state and vagal activity in females with IBS across the age spectrum.⁹ The findings that young children demonstrate some vagal activity relationships (eg, with psychological distress) but not all (eg, with pain symptoms) found in adults with IBS suggest that age and/or duration of FAP/IBS may play a role. Further studies in a postpubertal population are required to address this hypothesis. Consequently, our results should not be extrapolated to the adolescent population.

Limitations to our study include the exploratory nature of examining possible relationships between psychological measures and vagal activity (ie, the multiple comparisons carried out). Further studies are needed to confirm this relationship and if present, understand why in children it is only found in girls with FAP/IBS while it is found in adult women regardless of IBS status. The smaller sample size of boys versus girls in our study also dictates that

additional studies with a larger group of boys with FAP/IBS are needed to confirm our findings.

Alterations in ANS have been described in a number of pain disorders besides IBS including celiac disease, painful bladder syndrome, and interstitial cystitis.^{2,20} In the case of celiac disease, the ANS imbalance remains after treatment whereas the GI and pain symptoms resolve.² In IBS, GI symptoms may respond more to treatment than the pain. These observations underline the importance of the brain gut axis and the role of emotional/psychological factors in exacerbating pain symptoms.²⁰

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Figure 1. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)³¹ flow diagram for the current study.

Figure 2.

The scatterplot represents the relationship between LnHF and trait anxiety score for girls (**A**) and boys (**B**) in the FAP/IBS group (circles, dark black line) and HC (triangles, thin grey line). The line represents a liner fit.

Table 1

Demographics and Medication Use

	FAP/IBS N = 100	HEALTHY COMPARISON N = 62	P
Girls	70 (70%)	44 (71%)	
Age (years)	8.9 ± 1.1 *	9.3 ± 1.1	.05
Body mass index	17.2 ± 3.1	17.1 ± 2.9	
College degrees			
Mothers	45%	70%	.003
Fathers	75%	75%	
Insurance			
HMO/PPO	74%	73%	
Medicaid/CHIPS	14%	9%	
Other	5%	2%	
Not reported	7%	18%	
Medications			
Antacids, H ₂ blockers, proton pump inhibitors	32%	0%	
Laxatives	4%	0%	
Antispasmodic	2%		
Bronchodilator	0%	3%	

* Mean ± SD.

Table 2

Comparison of Vagal Activity as Measured by Heart Rate Variability, Comparison of Psychological Distress, and Pain and Stooling Results

	Girls			Boys		
	FAP/IBS N = 70	HC N = 44	P	FAP/IBS N = 30	HC N = 18	P
Heart rate variability *						
Vagal activity						
24 hour total	6.8 ± 1.0	6.9 ± .9	.69	7.1 ± .9	6.9 ± .6	.24
Night	7.5 ± 1.1	7.7 ± .9	.26	7.7 ± .9	7.6 ± .8	.83
Day	6.3 ± 1.1	6.2 ± 1.1	.64	6.5 ± .9	6.1 ± 1.0	.17
Sympathovagal						
24 hour total	1.11 ± .25	1.13 ± .26	.68	1.19 ± .30	1.19 ± .19	.10
Night	.90 ± .29	.89 ± .25	.64	.93 ± .25	.97 ± .20	.58
Day	1.39 ± .42	1.39 ± .35	.91	1.38 ± .36	1.49 ± .40	.27
Mean heart rate						
24 hour total	88.5 ± 8.1	88.4 ± 8.1	.68	85.4 ± 6.7	86.4 ± 5.8	.52
Night	74.7 ± 8.0	73.8 ± 8.3	.93	70.4 ± 7.3	70.3 ± 6.0	.95
Day	101.9 ± 12.3	101.0 ± 11.0	.87	97.2 ± 9.9	99.9 ± 10.1	.26
Psychological distress †						
Anxiety-Trait	35.1 ± 7.9	32.1 ± 6.8	.04	36.0 ± 8.4	34.6 ± 8.8	.53
Anxiety-State	25.5 ± 4.5	25.1 ± 3.6	.88	26.3 ± 4.9	25.4 ± 3.8	.42
Depression	9.6 ± 8.6	5.7 ± 6.2	.01	8.8 ± 7.0	4.7 ± 3.7	.037
Somatization	.88 ± .71	.40 ± .46	<.001	.80 ± .55	.61 ± .72	.07
Pain and stooling ‡	n = 63	n = 36		n = 25	n = 17	
Pain and interference						
Pain episodes	5.9 ± 5.0	.98 ± 1.9	<.001	4.3 ± 4.0	1.8 ± 3.2	.002
Pain severity	19.0 ± 16.9	5.9 ± 7.7	<.001	21.7 ± 20.4	11.8 ± 14.1	.038
Pain interference	.54 ± .44	.11 ± .2	<.001	.71 ± .6	.27 ± .36	.003
Stool frequency/consistency						
Stool frequency	7.1% ± 2.8	6.7 ± 2.4	.60	5.8 ± 2.3	6.1 ± 2.0	.47
Hard stool	20% ± 25	17% ± 21	.57	11% ± 13	12% ± 20	.54

	GIRLS			BOYS		
	FAP/IBS N = 70	HC N = 44	P	FAP/IBS N = 30	HC N = 18	P
Formed stool	62% ± 29	71% ± 28	.07	75% ± 17	73% ± 26	.85
Watery or mushy stool	18% ± 24	12% ± 19	.19	13% ± 15	15% ± 20	.78

* *P* values based on ANCOVA of heart rate variability indices controlling for age and BMI, stratified by child's gender.

[†] Due to variance heterogeneity in several of the variables, all the reported *P* values are based on Mann Whitney nonparametric test for 2 independent groups.

Table 3

Comparison of Slopes and Interactions at Night for Girls

	<i>FAP/IBS</i> <i>N</i> = 70		<i>HC</i> <i>N</i> = 44	
	β	(SE)*	β	(SE)*
Vagal activity, nocturnal				
Anxiety-Trait	-.055 ± .016	.001	.029 ± .019	.146 .002
Anxiety-State	-.009 ± .030	.76	.036 ± .039	.367 .48
Depression	-.033 ± .015	.039	.022 ± .022	.323 .06
Somatization	-.517 ± .190	.008	.481 ± .285	.099 .007
Sympathovagal, nocturnal				
Anxiety-Trait	.010 ± .004	.007	-.004 ± .006	.492 .036
Anxiety-State	.001 ± .007	.92	-.019 ± .011	.105 .26
Depression	.006 ± .004	.08	-.008 ± .006	.213 .041
Somatization	.036 ± .045	.43	-.119 ± .084	.167 .08

* β (SE) = Unstandardized coefficient (standard error).† PX = *P*-value or interactions within subjects.