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Multisite Pain is Highly Prevalent in Children with Functional Abdominal Pain Disorders and is Associated with Increased Morbidity

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Abstract

Objectives: To characterize the types of multisite pain experienced by children with functional abdominal pain disorders (FAPDs) and to examine differences in psychosocial distress, functional disability and health-related quality of life in children with multisite pain vs. abdominal pain alone.

Study design: Cross-sectional study of children ages 7-17 years (n=406) with pediatric Rome III FAPDs recruited from both primary and tertiary care between January 2009 and June 2018. Subjects completed 14-day pain and stool diaries, as well as validated questionnaires assessing abdominal and non-abdominal pain symptoms, anxiety, depression, functional disability and health-related quality of life.

Results: 295 (73%) children endorsed at least one co-occurring non-abdominal pain thus were categorized as having multisite pain with the following symptoms: 172 (42%) headaches, 143 (35%) chest pain, 134 (33%) muscle soreness, 110 (27%) back pain, 94 (23%) joint pain, and 87 (21%) extremity (arms and legs) pain. In addition, 200 children (49%) endorsed two or more non-abdominal pain symptoms. Participants with (vs without) multisite pain had significantly higher abdominal pain frequency ($P<0.001$) and severity ($P=.03$), anxiety ($P<0.001$), and depression

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($P < 0.001$). Similarly, children with multisite pain (vs. without) had significantly worse functional disability ($P < 0.001$) and health-related quality of life scores ($P < 0.001$). Increasing number of multisite pain sites ($P < 0.001$) was associated with increased functional disability when controlling for demographic and other clinical factors.

Conclusions: In children with FAPDs, non-abdominal multisite pain is highly prevalent and is associated with increased psychosocial distress, abdominal pain frequency and severity, functional disability, and lower health-related quality of life.

Keywords

Irritable bowel syndrome; overlapping pain; headaches; abdominal pain; children

Functional abdominal pain disorders (**FAPDs**) affect up to 20% of schoolchildren and adults worldwide and exert a significant social, emotional, and economic burden.^{1–5} Diagnostic biomarkers are not available, thus the diagnosis of FAPDs is dependent on a symptom-based diagnosis using pediatric Rome consensus criteria.⁶ FAPDs are associated with disruption of normal activity and decreased quality of life, although the functional impact of pain among children is highly variable.^{3, 7, 8}

Pain that occurs in more than one anatomical site, also known as multi-site pain, is also common in both children and adults.^{9–11} Multisite pain is associated with greater morbidity than single site chronic pain, including decreased physical and psychological functioning.^{9, 10} However, there has been limited investigation of multisite pain in children with FAPDs; yet in other pain conditions (e.g., chronic pediatric musculoskeletal pain), multisite pain is considered an important distinct pain entity that may influence functional outcomes and require personalized treatment approaches.^{9, 10} We hypothesized that in children with FAPDs, multisite pain would be more common than single site (i.e., abdominal only) pain. Furthermore, we hypothesized that children with FAPDs with (vs. without) multisite pain would have greater psychosocial distress (e.g., anxiety), abdominal pain, functional disability, and lower health-related quality of life. Last, we expected multisite pain would predict high disability in children with FAPDs in a multivariate model even after controlling for demographic, clinical, and psychosocial factors.

METHODS

This is a secondary data analysis. Children were identified from their participation in prior prospective studies of functional abdominal pain in our research group. Children were selected if they were ages 7–17 years with FAPDs. Only available baseline (prior to any intervention) data obtained between January 2009 and June 2018 were used. The Baylor College of Medicine Institutional Review Board approved all recruitment and study procedures. Informed consent was obtained from the parent and assent from the child.

Participants were originally identified from a large academic pediatric gastroenterology practice and general pediatrician offices within the same affiliated hospital system based on medical chart review for potential study participation. Chart review identified potential subjects based on the *International Classification of Diseases, Ninth Revision* codes of 789.0

(abdominal pain) or 564.1 (irritable bowel syndrome). Children were screened to determine if the abdominal pain was chronic (lasting ≥ 2 months). All participants were enrolled in studies using Rome III criteria as the studies commenced prior to Rome IV criteria (2016) being available. Using the Rome III criteria, participants were included in the study if they qualified as having either irritable bowel syndrome or functional abdominal pain based exclusively on baseline (prior to any intervention) pain and stool diaries.¹² In those with IBS, subtyping for IBS-constipation, IBS-diarrhea, IBS-mixed subtype, and IBS-unspecified was completed using stool form data.¹³

Children were excluded if chart review or screening identified: an organic gastrointestinal illness (e.g., inflammatory bowel disease); a significant comorbid systemic chronic health condition (e.g., diabetes); vomiting ≥ 2 times per month for the preceding 3 months (to exclude unidentified severe gastroesophageal reflux or upper gastrointestinal motor disorder); unexplained weight loss; hematochezia; current use of any medication that completely alleviated the pain; lack of fluency in English (as some of the questionnaires used were only available in English); and significant developmental delay (preventing questionnaire or diary completion).

Measures

Sociodemographic data were obtained via a questionnaire completed during their baseline visit capturing age, sex, and race/ethnicity data. The questionnaire considered Hispanic as a combined race/ethnicity category.

Multisite Pain.—Items from the Children’s Somatic Symptom Inventory specific to pain were used to assess multisite pain including headaches, chest pain, back pain, muscle soreness, joint pain, extremity (arms and legs) pain, and pain with urination.¹⁴ Participants rated “how much were you bothered” (0 – not at all; 1 – a little; 2- somewhat; 3- a lot; 4 a whole lot) by each assessed symptom in the last two weeks. Subjects who identified a minimum frequency of “somewhat” were considered to have pain in that site. The number of pain sites was summed. Children with at least one endorsed pain site (in addition to their abdominal pain) were coded as having multisite pain.

Psychosocial Distress.—Participants completed The Behavior Assessment System for Children–Second Edition; a psychometrically robust instrument used to measure a range of behavioral and emotional problems in children.¹⁵ T scores with a mean of 50 and SD are derived for each scale. Anxiety and depression scales from the child self-report forms was evaluated.

Gastrointestinal Symptoms.—All participants completed 14-day pain and stool diaries as we have previously reported.^{16, 17} Children rated their abdominal pain severity 3 times a day using an 11 point numerical rating scale with the anchors 0 “no pain at all” and 10 “the worst pain you can imagine.” Mean pain severity was defined as each child’s average pain severity over the course of 2 weeks when pain was present. Pain frequency was defined as the number of pain episodes a child reported over the 2- week period.

Functional Disability.—Participants completed the Functional Disability Inventory, which is a 15-item questionnaire that measures the degree to which children have difficulty performing physical, social, and recreational activities due to abdominal pain.¹⁸ The total scores range from 0 to 60 with higher scores reflecting higher levels of perceived disability.¹⁸

Quality of Life.—A subset of 298 participants (not all participants were asked to complete the measure as part of their baseline assessment) completed the Pediatric Health-Related Quality of Life 4.0 Generic Core Scales to assess health-related quality of life (**HRQOL**). This is a 23-item, validated questionnaire used in healthy populations and in those with medical conditions (including FAPDs).^{19, 20} Total HRQOL as well as subscales (Physical, Emotional, Social Function, School Function, Psychosocial) scores were used for analysis. Scores range from 0 to 100, with higher scores reflecting better HRQOL.^{19,20}

Statistical Analyses

IBM SPSS Statistics version 27, 2020 (IBM Corporation, Armonk, New York) was used for statistical analysis. To characterize the number and type of multisite pain reported by children, frequencies of each individual pain site, mean number of pain sites, and proportion of children with multisite vs single site pain were computed. As the data are non-parametric, results are presented as median [25-75%].

To determine whether children with FAPDs with (vs. without) multisite pain would have greater psychosocial distress, functional disability, and lower HRQOL, we conducted Chi-square analysis to compare proportions and Mann-Whitney U testing for continuous data between the two groups. A multivariate model controlling for demographic, clinical, and psychosocial factors was tested to examine whether multisite pain would predict high functional disability in children with FAPDs. Linear regression analysis using the enter method was completed with functional disability as the dependent variable and independent variables including age, sex, diagnosis (IBS vs. FAP), abdominal pain frequency, mean abdominal pain intensity, anxiety, depression, and presence of multisite pain.

P-values < 0.05 were considered to be significant. There were missing data as not all subjects across studies completed all of the same evaluated measures. We have indicated the number of subjects completing each measure in Tables 1–4.

RESULTS

Sample Characteristics

Sample characteristics are shown in Table I; 406 children with FAPDs (median age = 10 years) were included of whom the majority were female (64%). Two hundred eighty-four (70%) had IBS and 122 (30%) had FAP. Of those with IBS, 127 (44.7%) had IBS-constipation, 126 (44.4%) had IBS-unsubtyped, 21 (7.4%) had IBS-diarrhea, and 10 (3.5%) had IBS-mixed type.

Prevalence and Type of Non-Abdominal Multisite Pain in Children with FAPDs

As shown in Table 2, the majority of children (73%) endorsed at least one non-abdominal pain symptom and thus were classified as having multisite pain. In descending order of frequency, multisite pain locations included headaches, chest pain, muscle soreness, back pain, joint pain, and extremity (arms and legs pain), and pain with urination.

A similar proportion of children with IBS (208/284; 73.2%) and FAP (87/122; 71.3%) reported multisite pain. We did not identify a statistically significant difference in the frequency of multisite pain based on IBS subtype with 97 (76%) of those with IBS-constipation, 86 (68%) IBS-unsubtyped, 16 (76%) IBS-diarrhea, and 9 (90%) of those with IBS-mixed type having multisite pain. Adolescents (68/73; 93%) had a significantly higher frequency of multisite pain than younger children (227/333, 66%; $P<0.001$). Girls and boys had a similar frequency of multisite pain (194/260, 75% vs. 100/145; 69%; $P=0.22$).

Differences in Psychosocial and Physical Functioning in Children With Vs Without Multisite Pain

Table 3 shows scores by multisite pain status on measures of morbidity including abdominal pain frequency and intensity, anxiety, depression, functional disability, and HRQOL. Participants with multisite pain had greater abdominal pain frequency ($P<0.001$), abdominal pain intensity ($P=0.03$), anxiety ($P<0.001$; though both groups had mean scores in the normal range), depression ($P<0.001$; though both groups had mean scores in the normal range), functional disability ($P<0.001$), and lower overall HRQOL ($P<0.001$) compared with those with single site abdominal pain. Within the HRQOL sub-domains, children with multisite pain had significantly worse scores (all $P<0.001$) in physical functioning, emotional functioning, and school functioning compared with children with single site abdominal pain only, whereas social functioning was comparable between groups.

Multivariate Analyses

Table 4 shows a multivariate analysis using multiple linear regression to evaluate the relationship between number of non-abdominal pain sites and functional disability, controlling for demographic and clinical factors (age, sex, abdominal pain frequency, abdominal pain intensity, anxiety, and depression). In the final adjusted model more non-abdominal pain sites predicted higher functional disability ($P<0.001$ and Beta 0.33).

DISCUSSION

Though multisite pain has been associated with greater morbidity in patients with chronic pain, there is sparse information regarding the presence of multisite pain in children with FAPDs. We identified that non-abdominal multisite pain was highly prevalent (>70%) in a large cohort of children with FAPDs. Headaches were the most frequently reported symptom, followed by chest pain and other musculoskeletal-related pain. In children with FAPDs with (vs. without) multisite pain we identified a range of negative consequences including higher abdominal pain frequency, abdominal pain intensity, functional disability, lower HRQOL, and higher psychosocial distress (anxiety and depression, though mean scores for both groups were in the normal range). When controlling for demographic

and clinical factors in a multivariate analysis we identified that more multisite pain sites were associated with greater functional disability. Though further prospective clinical investigations are needed, these data suggest the presence of multisite pain may be common and associated with increased morbidity in children with FAPDs.

The prevalence and type of multisite pain in children with FAPDs has not been well characterized. Our findings provide a preliminary understanding of children's experience of co-occurring non-abdominal pain, showing frequent endorsement of headache and musculoskeletal pain sites. Headaches were the most common non-abdominal pain site in our cohort. Our findings are supported by those of a recent cross-sectional retrospective study of 235 children with FAPDs that found approximately 70% have chronic headaches; however, other pain sites were not assessed.²¹ The high prevalence of multisite pain in our study suggests multisite pain is common but not universal in children with FAPDs. Future studies are needed to better characterize multisite pain in children with FAPDs to understand the duration of symptoms, severity, course, and impact.

Data available in adults with IBS also supports our findings. Up to 65% of adults with IBS have overlapping fibromyalgia (characterized by multisite musculoskeletal pain).^{22, 23} Adults with IBS (vs. general population) also have a significantly higher prevalence of co-occurring migraines and headaches.²⁴ Though we did not identify a sex-based difference in our cohort, it should be noted that in the above-cited adult studies, women composed the majority of the evaluated study populations.

Our findings demonstrated that children with FAPDs with (vs. without) multisite pain have higher anxiety and depression scores, though group means were both within the normal range. As this study is cross-sectional, we cannot determine whether there is a causal relationship between multisite pain and psychosocial distress. Nevertheless the study findings are supported by those of Little et al who identified increasing non-gastrointestinal symptoms were associated with an increased likelihood of depression in children with chronic abdominal pain.²⁵ Greater psychosocial distress is believed to be a risk factor for the development of multisite pain.¹¹ These psychosocial factors may contribute to enhanced pain perception either via peripheral or central sensitization mechanisms as part of a multifactorial process with additional factors such as environmental events and genetic variability playing a role.²⁶ Longitudinal studies in children with FAPDs may help further delineate the directionality of the relationship between psychosocial distress and multisite pain.

We also found that children with (vs without) multisite pain reported greater functional disability, similar to findings in available adult and pediatric chronic pain literature. For example, in an observational study of 166 children of various pain types (acute, pre-surgical, and chronic) increasing multisite pain was associated with greater functional impairment.⁹ Within FAPD research specifically, an increase in non-gastrointestinal symptoms in children with FAPDs, including non-pain related symptoms such as dizziness and blurred vision, have been reported.^{27, 28} Though not specific to pain, higher non-gastrointestinal symptoms in children with FAPDs also have been associated with higher morbidity including greater abdominal pain severity and greater functional disability.^{27, 29} Overall, the strong

relationship between greater multisite pain and higher functional disability when controlling for other demographic and clinical factors suggests that more research is needed to understand how to optimally assess and treat multisite pain in children with FAPDs.

In children and adolescents, chronic pain negatively affects multiple domains that comprise HRQOL including: school attendance; social, physical, and athletic activities; and emotional functioning.³⁰ We found that children with FAPDs with (vs. without) multisite pain have lower HRQOL overall and in several sub-domains. Findings regarding the relationship between multisite pain and HRQOL have been equivocal in published literature in children with chronic pain. A previous population-based cross-sectional study in ~3000 Danish adolescents identified that those with multisite pain had decreased HRQOL vs. those without pain but not vs. those who reported a single region of pain.³¹ A separate study using an online survey of middle and high-school students identified that those with multisite pain (vs. single site pain) did have lower HRQOL.³²

There are some limitations to our study. As it was cross-sectional, we are not able to establish causal relationships between multisite pain and psychosocial and functional morbidity. The measure of multisite pain we used did not capture symptom duration beyond two weeks and therefore we are unable to determine whether co-occurring pain symptoms were acute or chronic, which may have implications for long-term prognosis in children with FAPDs. Another limitation relates to potential increased pain awareness by asking children to complete daily pain diaries. Future studies may include parent reports of child pain and functioning.

There are also several strengths to this study which evaluated multisite pain in children with representation across a wide range of ages and race/ethnicities, supporting generalizability of the results. In addition, all included subjects met pediatric Rome III criteria, and we used well-established, validated measures of abdominal pain, psychosocial distress, functional disability, and quality of life, increasing the rigor of the evaluation.

In conclusion, a high proportion of children with FAPDs have multisite pain. Multisite pain is associated with higher levels of psychosocial distress (anxiety and depression), abdominal pain frequency and severity, functional disability, and lower quality of life. Though further prospective longitudinal studies would significantly advance the clinical science related to multisite pain in children with FAPDs, our findings suggest those caring for children with FAPDs should identify whether multisite pain is present, and if identified, consider an early holistic treatment approach (considering physical, social, and emotional wellbeing) which may help address and/or prevent psychosocial distress and functional disability.

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Abbreviations:

FAPDs	Functional Abdominal Pain Disorders
HRQOL	Health-related Quality of Life

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Table 1.

Characteristics of the Study Population

Variable	Median [25-75%ile] or n (%)
Age (years)	10 [8-12] years
<u>Sex</u>	
Female	260 (64.2%)
Male	145 (35.8%)
<u>Race/Ethnicity</u>	
White	234 (57.6%)
Black	59 (14.5%)
Hispanic	89 (21.9%)
Asian	14 (3.4%)
More than one	6 (1.5%)
<u>FAPD subtype</u>	
IBS	284 (70%)
FAP	122 (30%)
Abdominal pain episodes/2 weeks	11 [5-19]
Abdominal pain intensity (0-10)	3.1 [2.3-4.2]
Anxiety (T-score)	51 [43-60]
Depression (T-score)	45 [42-51]
Functional Disability	8 [3.75-18]
PedsQL Total Score	81.5 [68.2-89.4]

* Data missing for the following variables: Age (n=1), Sex (n=1), Race/Ethnicity (n=4), Anxiety/Depression (n=6), Functional Disability (n=4). n=298 completed PedsQL measures.

Table 2:

Multisite Pain Characteristics in a Cohort of Children with Functional Abdominal Pain Disorders (n=406)

Multisite Pain Characteristic	N (%)
Any non-abdominal Multisite Pain	295 (73%)
More than one non-abdominal multisite pain site	200 (49%)
Number of non-abdominal pain sites in those with multisite pain	2 [1-3]*
Non-abdominal Multisite Pain Locations	
Headaches	172 (42%)
Chest pain	143 (35%)
Muscle soreness	134 (33%)
Lower back pain	110 (27%)
Joint pain	94 (23%)
Extremity (arms and legs) pain	87 (21%)
Pain with urination	30 (7%)

* Median [25-75%]

Table 3:

Comparisons between Children with FAPDs with vs. without Multisite Pain (MP) on Abdominal Pain, Psychosocial Distress, Functional Disability, and Health-Related Quality of Life

	With MP (n=295)	Without MP (n=111)	P-Value
Abdominal Pain Episodes/ 2 wk.	12 [6-20]*	7 [3-14]	<0.001
Abdominal Pain Intensity (0-10)	3.2 [2.3-4.2]	2.8 [2.2-3.9]	0.03
Anxiety (T-score)	54 [45-62]	45 [39-54]	<0.001
Depression (T-score)	46 [42-53]	43 [41-47]	<0.001
Functional Disability	10 [5-19]	5 [1-9]	<0.001
PedsQL Total Score	77.2 [65.2-87]	88 [81.5-93.4]	<0.001
PedsQL Physical Function	78.1 [62.5 – 90.6]	90.6 [81.3 - 96.9]	<0.001
PedsQL Emotional Function	70 [50 – 85]	90 [80 - 95]	<0.001
PedsQL Social Function	95 [80 – 100]	95 [85 - 100]	0.27
PedsQL School Function	75 [60 – 85]	85 [75 - 95]	<0.001
PedsQL Psychosocial Function	76.7 [63.3 – 86.7]	88.3 [80 – 93.3]	<0.001

* Median [25-75%]

Note: n=298 completed PedsQL measures (216 with and 83 without MP)

Table 4:

Multivariate Linear Regression Model predicting functional disability related to the number of non-abdominal pain sites while controlling for abdominal pain characteristics, depression, anxiety, sex, and age

Factor	B [95% CI]	Beta	P-value
(constant)	-7.58		0.04
Number of Non-Abdominal MP Sites	1.8 [1.3-2.3]	.33	<0.001
Abdominal Pain Episodes/ 2 wk.	.12 [.03-.021]	.12	.008
Abdominal Pain Intensity (0-10)	.76 [.13-1.38]	.11	.02
Depression (T-score)	.13 [.01-.024]	.11	.04
Anxiety (T-score)	.09 [-.004-.18]	.1	.06
Sex (1=Male/2=Female)	.22 [-1.8-1.8]	.01	.81
Age	.03 [-0.31-.36]	.01	.88

$R^2 = 0.28$