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Spectrum of Functional Abdominal Pain Disorders in Children and Their Clinical, Social Characteristics: A Cross-Sectional Study

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ABSTRACT

Background/Aims: Pediatric functional abdominal pain disorders (FAPDs) subtypes; functional dyspepsia (FD), irritable bowel syndrome (IBS), functional abdominal pain-not otherwise specified (FAP-NOS), and abdominal migraine (AM) are influenced by demographic and social factors. The study aimed to evaluate the spectrum and demographic and social factors associated with FAPD subtypes.

Methods: Consecutive children (< 18 years) diagnosed with FAPD subtypes according to ROME-IV criteria between April 2018 and March 2020 were included. The clinical, demographic, and social parameters were analyzed between various subtypes of FAPD, and factors responsible for severe symptoms were studied.

Results: A total of 479 children (mean age 12.34 ± 3.82 years, 60% boys) were included. FAP-NOS (63%) was the most commonly diagnosed subtype followed by IBS (17.4%) and FD (15%). The age at presentation, site of pain, duration of symptoms, and associated symptoms were significantly different among the three main subtypes ($p < 0.001$). Stressors could be identified in 39.3% and academic pressure (22.3%) was the most common. Family members with functional disorders (OR: 2.21, 95% CI: 1.31–3.42, $p = 0.02$), presence of stressors (OR: 2.03, 95% CI: 1.14–3.65, $p = 0.016$), and rural origin (OR: 1.75, 95% CI: 1.08–2.83, $p = 0.023$) predicted severe symptoms.

Conclusions: FAP-NOS is the most common FAPD subtype in children in India. Children with FAP-NOS are much younger than other subtypes of FAPD. The presence of stressors and functional disorders in family members could be associated with severe symptoms. However, it mandates more prospective studies to validate the findings.

1 | Introduction

Functional abdominal pain is a common disorder seen in children with a worldwide pooled prevalence of 13.5% [1]. Rome IV classified pain-related functional gastrointestinal disorders (FGIDs) as functional abdominal pain disorders (FAPDs) which were further classified as functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), and functional abdominal pain not otherwise specified (FAP-NOS) [2]. FAPD significantly affects the quality of life and has a severe impact on the emotional and financial conditions of the family [3–5]. Rome IV involves the development of a multidimensional clinical profile (MDCP), which classifies each functional disorder into five components: categorical Rome diagnosis, subclassifications, the impact of the disorder on the patient, psychosocial influences, and biomarkers. This emphasizes the importance of psychological and social factors in the effective management of FAPD [6].

Rome IV does not require extensive investigations to rule out organic etiology, and the diagnosis of FAPD can be made by clinical history, examination, and appropriate investigations [7]. In spite of effectively eliminating red flags, abdominal pain in FAPD has a varied spectrum of presentations with respect to the duration of symptoms, location of pain, frequency of symptoms, associated symptoms, and quality of life impairment.

Although a few studies showed female predominance of FAPD in children, the pediatric literature from developing nations to substantiate this finding is scarce [8, 9]. Psychosocial factors such as stress, abuse, psychiatric disturbance like anxiety and depression, coping style, etc., contribute to the spectrum and outcome of FAPD in children [10]. High levels of anxiety and the past experience of stressful events have been believed to amplify the symptom experience in children [11]. Children with FAPD also exhibit more extraintestinal symptoms such as headache, fatigue, and sleep disturbances [12].

Social factors also impact the symptoms in pediatric FAPD and are more commonly seen when the parents are suffering from chronic pain. In a study, more severe pain, school absenteeism, and frequent health care visits were seen more commonly in children with parents having IBS as compared to control families [13]. Most of the studies in FAPD either deal with pathophysiology, etiology, or management aspects. However, there are not many studies describing the spectrum of clinical presentation of FAPD in children from developing countries. The study aimed at evaluating the various clinical aspects of abdominal pain, associated symptoms, and social factors in pediatric FAPDs from a tertiary center in a developing country.

2 | Materials and Methods

In this cross-sectional study, consecutive children (< 18 years of age) diagnosed to have FAPDs fulfilling Rome IV criteria from April 2018 to March 2020 in the Pediatric Gastroenterology department were included in this study. The center in which the study was performed is a referral center that caters to almost 4–6 nearby states, as there is no other pediatric gastroenterology center in the public sector in this vast area. All the children recruited in the study were referred by General practitioners from both rural and urban areas. The clinical assessment was supervised, and the diagnosis of all the children included in the study was confirmed by trained Pediatric Gastroenterologists with more than 5 years of experience.

3 | Evaluation

Children with age < 18 years, with complaints of abdominal pain at least for 2 months satisfying ROME IV criteria either in the first or subsequent visits were included in the study. In smaller children (≤ 7 years), the history was obtained from the parents. The children with "acute abdomen," pain requiring hospitalization, presence of "red flags" such as blood in stools, persistent vomiting, dysphagia, odynophagia, unintentional weight loss, growth delay, and family history of inflammatory bowel diseases or with history and examination suggesting a possibility of organic diseases were excluded from the study. The basic blood investigations were performed in all cases and that includes inflammatory markers such as complete blood counts (CBC), ESR, CRP, total protein and albumin, urine routine examination, stool for occult blood. Cross-sectional imaging (ultrasonogram [USG]), and endoscopy (upper GI endoscopy with or without ileocolonoscopy) were performed as and when a possibility of organic disease was considered strongly by the treating clinicians. In case, there was a possibility of organic etiology of abdominal pain at first visit, but when sufficiently ruled out by thorough investigations, the patients were still included in the study. Children diagnosed of FAPDs (FAP-NOS, IBS, FD, and AM) were reviewed and data were collected regarding age, gender, abdominal pain (site, frequency, duration), associated symptoms, extra-intestinal manifestations, native of rural or urban area, birth order, family history of functional pain disorders/abdominal pain, history of past antitubercular therapy (ATT), presence of stressors, anthropometry, pallor, edema and abdominal examination findings were noted. The pain is described in terms of site of pain (epigastric, right hypochondrium, left hypochondrium, right lumbar, left lumbar, periumbilical, hypogastric, right and left iliac fossa), frequency of pain (daily, more than once a week, once a week, once in more than a week). The frequency is termed variable when the frequency of pain is not categorized in either of the groups, duration of the episode and duration of the pain, associated symptoms.

3.1 | Ethics

The study conforms to the principles of the 1975 Declaration of Helsinki. The study was conducted after taking due approval from the institutional ethics committee (IEC) and informed consent was obtained from either parent before all intervention.

4 | Statistical Analysis

Descriptive statistical analysis was performed using SPSS software for windows version 20 (IBM, Chicago, USA). Variables are expressed as mean and standard deviation and proportions. Independent t test or Mann–Whitney U test was applied when analyzing continuous data, and Chi-square/Fisher's exact test was applied when analyzing nominal variables. Multivariate binary logistic regression was performed to analyze the predictors of severe pain. $p < 0.05$ was considered significant.

5 | Results

Among 3973 children visited the pediatric gastroenterology outpatient services during the study period, 479 (12.05%) children diagnosed as FAPDs were included in the study. The mean age was 12.3 ± 3.82 years (range: 4–18 years) with the male to female ratio 287 (59.9%): 192 (40.1%). Of the 479 children, 302 (63%) were diagnosed as FAP-NOS, 72 (15%) as FD, 83 (17.4%) as IBS, and 22 (4.6%) children were diagnosed with more than one FAPD (Figure 1).

5.1 | Pain Characteristics

The baseline characteristics including familial and social factors, and stressors of all the included children are shown in Table 1. The age at presentation, duration of symptoms, site of pain, and associated symptoms were significantly different between the

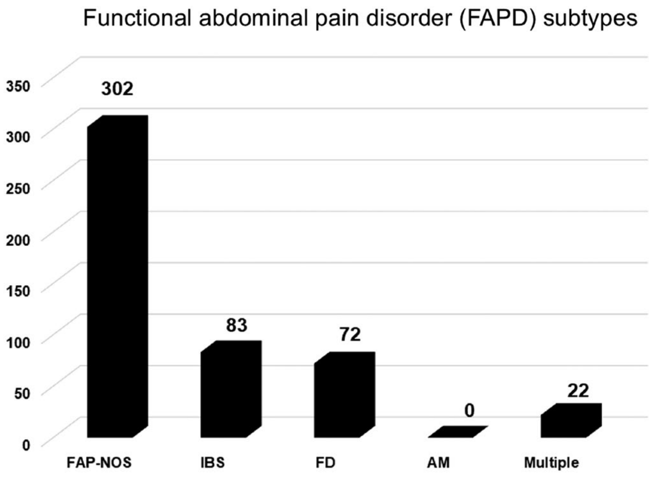

FIGURE 1 | Prevalence of different subtypes of functional abdominal pain disorders.

groups; FD, FAP-NOS, and IBS (all $p < 0.001$) (Table 2). Post hoc analysis of these factors between two groups showed, age at presentation was significantly lower in FAP-NOS as compared to FD (11.05 ± 3.56 vs. 13.78 ± 3.42 years, $p < 0.001$) and IBS (11.05 ± 3.56 vs. 15.02 ± 2.92 years, $p < 0.001$). Duration of symptoms of IBS was much longer as compared to FD (22.29 ± 23.47 vs. 12.32 ± 12.02 months, $p = 0.002$) and FAP-NOS (22.29 ± 23.47 vs. 14.56 ± 16.16 months, $p = 0.001$). Post hoc analysis regarding the site of pain showed FD had significantly higher epigastric pain compared to IBS and FAP-NOS ($p < 0.001$), FAP-NOS had higher periumbilical pain as compared to FD and IBS ($p < 0.001$), and IBS had higher hypogastric pain compared to FD and FAP-NOS ($p < 0.001$). Regarding associated symptoms, FD had associated vomiting much higher than FAP-NOS and IBS ($p < 0.001$) and IBS had higher associated loose stools and constipation compared to FD ($p < 0.001$) and FAP- NOS ($p < 0.001$).

5.2 | Social Factors

The stressors could be identified in 39.3% of cases. Among the stressors, the most common was related to academic/school pressure (22.3%), followed by stress from parental anxiety (6.8%), pressure related to sibling performance (4.1%), and conflicts/bullying among the friends (2.1%). Extra-intestinal symptoms/disease were seen in 48 (10.0%) children, and the most commonly seen were body aches ($n = 12$), headache ($n = 4$), and syncope/pseudoseizures ($n = 2$). The pain characteristics and other factors for different diagnoses of FAPD are shown in Table 2.

5.3 | Imaging Findings

At least one USG was done in 401 (83.7%) of children either elsewhere or at the time of evaluation in our center. None showed any significant finding that can contribute to the abdominal pain However, nonspecific findings such as subcentimetric mesenteric lymph nodes were seen in 63 (15%), asymptomatic gallstones in 12 (none had biliary colic), renal findings in 6 (prominent left pelvis) (1), absent right kidney (1), bilateral renal enlargement (1), ectopic left kidney (1), Horse-shoe kidney (1), nonobstructing renal calculus (1) bowel thickening in two (not substantiated by CT scan later), liver enlargement in four, and splenomegaly in one. CECT abdomen was done in 73 (15.2%) children, which was normal in 56 (77%). Nonspecific findings such as suspicion of small bowel enhancement in 13 and subcentimetric lymph nodes were seen in 30. However, on follow-up, none showed any feature of organic pathology, and follow-up imaging was normal. Upper GI endoscopy was done in 12, lower GI endoscopy in five, whereas both were done in two. All 14 upper GI endoscopies and six of seven lower GI endoscopies were normal except for one that showed a juvenile polyp in the rectum.

5.4 | Predictors of Severity

The pain was considered severe ($n = 148$, 32.2%) when the frequency of pain was every day and/or when the duration of pain was more than 12 months. The factors like nativity, presence of stressors, family history of functional pain disorders, presence of extra-intestinal symptoms, birth order, and subtype diagnosis were analyzed between severe and nonsevere pain (Table 3) (Figure 2). Multivariate binary logistic regression was done for

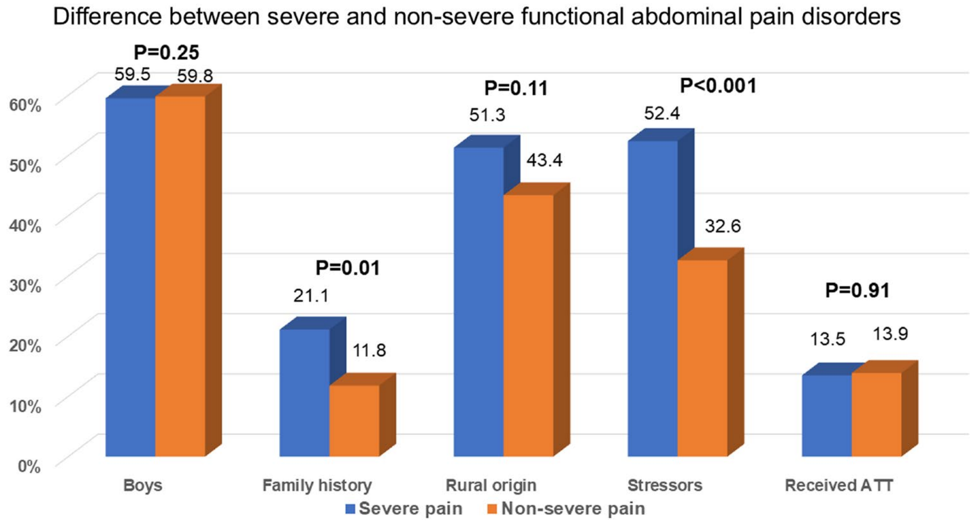

FIGURE 2 | Difference between severe and nonsevere pain with respect to factors such as gender, nativity, presence of stressors, family history of functional disorders, and previous antitubercular therapy.

TABLE 1 | Baseline characteristics of children diagnosed fapd ($n = 479$).

Mean age in years		**12.34 ± 3.82 (range, 4–18)**
Gender	Male: female	287 (60%): 192 (40%)
Site of pain ($n = 478$)[a]	Periumbilical	291 (56.5%)
	Epigastric	83 (16.1%)
	Hypogastric	36 (7%)
	Right hypochondriac	11 (2.1%)
	Left hypochondriac	7 (1.4%)
	Right lumber	2 (0.4%)
	Left lumber	3 (0.6%)
	Right iliac	7 (1.4%)
	Left iliac	4 (0.8%)
	Variable	34 (6.6%)
Frequency of pain ($n = 474$)[a]	Daily	90 (19%)
	> Once a week	103 (20%)
	Once a week	86 (18.1%)
	Once in > 1 week	131 (27.6%)
	Variable frequency	64 (13.5%)
Duration of episode (min)		37.74 ± 86.75
Duration of symptoms (mo)		15.36 ± 17.20
Associate symptoms	Vomiting	60 (12.5%)
	Loose stools	46 (9.6%)
	Constipation	78 (16.3%)
Identification of stressors		185/473 (39.1%)
Diagnosis	FD	72 (15%)
	IBS	83 (17.3%)
	FAP-NOS	302 (63%)
	Multiple	22 (4.6%)
History of antitubercular Rx		66 (13.9%)
Nativity ($n = 478$)[a]	Rural vs. urban	217 (45.4%) vs. 261 (54.6%)
Family history		70 (14.6%)
Mean number of siblings		1.76 ± 0.69
Birth order		1.55 ± 0.65
Weight z score		−0.49 ± 1.23
Height z score		−0.27 ± 1.35
BMI z score		−0.46 ± 1.16
Mean hemoglobin (g/L)		12.45 ± 1.54
Mean platelets ($10^5/mm^3$)		2.40 ± 0.79
Mean ESR (first hour)		16.01 ± 10.57

[a]Data not available for one case each regarding nativity and site of the pain, and five cases for frequency of pain.

TABLE 2 | Pain characteristics and social factors for various diagnoses of fapd ($n=457$).

		FD ($n=72$)	IBS ($n=83$)	FAP-NOS ($n=302$)	p
Age (years)		13.78 ± 3.42	15.02 ± 2.92	11.05 ± 3.56	< 0.001
Gender	Male: female	37: 35	48: 35	185: 117	0.151
Number of siblings		1.74 ± 0.626	1.90 ± 0.75	1.72 ± 0.66	0.161
Site of pain	Periumbilical	5 (6.9%)	44 (53%)	236 (78.4%)	< 0.001
	Epigastric	60 (83.3%)	2 (2.4%)	6 (2%)	
	Right hypochondriac	3 (4.2%)	1 (1.2%)	7 (2.3%)	
	Left hypochondriac	1 (1.4%)	1 (1.2%)	6 (2%)	
	Right iliac	1 (1.4%)	1 (1.2%)	3 (1%)	
	Hypogastric	0	27 (32.5%)	8 (2.7%)	
	Variable	2 (2.8%)	7 (8.4%)	35 (13.6%)[a]	
Frequency of pain	Daily	15 (20.8%)	14 (16.9%)	55 (18.5%)	0.148
	> Once a week	22 (30.6%)	18 (21.7%)	61 (20.5%)	
	Once a week	12 (16.7%)	13 (15.7%)	52 (17.5%)	
	Once in > a week	14 (19.4%)	27 (32.5%)	87 (29.3%)	
	Variable	9 (12.5%)	11 (13.3%)	42 (14.1%)	
Duration of episode (min)		35.28 ± 81.72	27.61 ± 27.33	45.11 ± 99.96	0.644
Duration of symptoms (mo)		12.32 ± 12.02	22.29 ± 23.47	14.56 ± 16.16	< 0.001
Associated symptoms	Vomiting	25 (34.7%)	2 (2.4%)	27 (8.9%)	< 0.001
	Diarrhea	0	36 (43.4%)	2 (0.7%)	
	Constipation	3 (4.2%)	41 (49.4%)	20 (6.6%)	
Nativity	Rural vs. urban	29: 43	41: 42	139: 163	0.558
Family history		4 (6%)	15 (18.8%)	44 (15.3%)	0.015
Presence of stressors		31 (43.1%)	35 (42.2%)	112 (37.8%)	0.805
Extra intestinal symptoms		7 (11.9%)	12 (16.2%)	36 (13.8%)	0.286
Weight (z score)		−0.56 ± 1.30	−0.17 ± 1.48	−0.55 ± 1.15	0.125
Height (z score)		−0.22 ± 1.10	0.05 ± 1.46	−0.35 ± 1.39	0.061
BMI (z score)		−0.56 ± 1.34	−0.35 ± 1.39	−0.47 ± 1.05	0.722

[a]Right lumber 3, left lumber 2, left iliac 5.

various parameters, of which the presence of stressors (OR: 2.21, 95% CI: 1.31–3.42, $p=0.020$), family history of functional pain disorders (OR: 2.03, 95% CI: 1.14–3.65, $p=0.016$), and rural origin (OR: 1.75, 95% CI: 1.08–2.83, $p=0.023$) predicted severe symptoms.

5.5 | Discussion

In the present study, FAP-NOS is the most common subtype (63%) of FAPDs, with age at presentation much younger than the children with FD and IBS. Children with IBS had longer duration of symptoms and higher family history of functional disorders among their family members compared to children with FD and FAP-NOS.

A meta-analysis with respect to epidemiology by Korterink et al. showed IBS is the most prevalent FAPD in children, unlike the present study, which showed FAP-NOS was much higher than other subtypes [1]. An Indian study of 1115 adolescents showed 112 children had FGID, which, on the contrary, showed FD as the most common sub-type of FAPD [14]. There are even studies from the Western population where AM is the most common FAPD in children [15, 16]. As most of the epidemiological studies are either community-based or school-based, hospital-based studies are fewer. One such hospital-based prevalence study from the United States showed 13% of the children attending the clinics had functional abdominal pain, and 11% had IBS [17].

The higher prevalence of FAP-NOS in the present study could be attributed to a lower mean age (12.34 ± 3.42 years) of the study

TABLE 3 | Comparison of parameters between children with severe and nonsevere pain.

	Severe pain (n = 148)	Non severe pain (n = 311)	p
Age	12.14 ± 3.80	12.86 ± 3.84	0.570
Gender (male: female)	88: 60	186: 125	0.250
Family history (%)	**30/142 (21.1%)**	**35/296 (11.8%)**	**0.010**
Nativity (rural vs. urban)	76: 72	135: 176	0.110
Weight (z score)	−0.48 ± 1.18	−0.50 ± 1.26	0.870
Height (z score)	−0.20 ± 1.27	−0.50 ± 1.26	0.410
BMI (z score)	−0.54 ± 1.11	−0.41 ± 1.20	0.270
Birth order (1:2:3:4)	64: 58: 4:0	138: 109: 18: 3	0.270
Presence of stressors (%)	**77/147 (52.4%)**	**100/307 (32.6%)**	**< 0.001**
Children recieved antitubercular therapy (%)	20/148 (13.5%)	43/309 (13.9%)	0.910
Diagnosis	FD 23	FD 47	0.670
	IBS 23	IBS 57	
	FAP-NOS 91	FAP-NOS 194	
	Multiple 7	Multiple 12	
Extra intestinal symptoms	16/127	37/266	0.720

Note: Significant values (p < 0.05) are marked bold.

population as compared to a few other studies from Asia with a higher mean age (14.4, 16.6 years) reporting IBS as a more common FAPD compared to FAP-NOS [18, 19]. The mean age of children with IBS and FD is significantly higher than that of children with FAP-NOS in our study. In another study from Brazil (n = 223), almost 70% of the FGID cases fell into the FAP-NOS category [20]. The mean age of the children in that study was 8.3 years only. The scenario is similar even in hospital-based studies. In a study by Spee et al., the data of 295 FAP children was collected from 53 general practitioners, where the mean age was 8.3 years, similar to our study. The most common sub-type of FAPD was FAP (53.8%) followed by IBS (38.5%) and FD (7.7%) [21]. We have also included younger children (4–18 years) and our results are similar to the study by Spee et al. [21] The prevalence of FAPD was higher in girls than boys based on a meta-analysis of 24 studies with the odds ratio 1.5 (95% CI: 1.3–1.7, p < 0.001), contrary to the gender prevalence of our study [1]. However, none of the series from India are included in the meta-analysis. Our study showed FAPDs to be much higher in boys (60%) than in girls, similar to certain other studies from India [14, 22]. It is not clear if the studies from India, in reality, represent higher prevalence of FAPD in males or referral bias [23]. Several reasons could be hypothesized for the longer symptom duration of IBS in this study. Firstly, the diagnosis of IBS is challenging compared to FAP-NOS due to the associated symptoms like diarrhea and/or constipation. As per the published literature, only 15% of the general practitioners were aware of the diagnostic guidelines of IBS, and almost half the GPs were unsure of the diagnosis of IBS [24]. This could have possibly led to delayed referral. Secondly, the mean age of the IBS children was much higher than that of the children with FAP-NOS in our study (15.02 vs. 11.05 years). As the IBS children are mostly adolescents, they tend to exhibit more denial and avoidance of their illnesses due to their developmental stage, sense of independence, and lack of understanding of their own illnesses [25].

The epidemiological studies in adults regarding the FGIDs showed prevalence is more in the urban population than the rural population [26]. However, the studies in children did not suggest the similar findings. The similar prevalence of FAP is noted in both the urban and rural populations in Malaysia with 11% and 9%, respectively [27, 28]. The prevalence study of FAPD in adolescents in Sri Lanka also did not show any significant difference between rural and urban (43% vs. 57%, p = 0.22) [29]. The center in which the study was performed caters predominantly to the most populous state and neighboring states. The literacy rate and socioeconomic status of the urban population of this areas is much higher than the rural population [30]. Parental factors, especially socioeconomic status and education status of the parents, have shown to play a significant role in the severity of symptoms in FAPD [31]. Hence, it is possible that the children from a rural background have more severe symptoms. Another likely reason could be that the children with more severe symptoms were preferentially brought to our center and those with milder symptoms were ignored by parents due to socioeconomic reasons. On the contrary, the urban population with better literacy and socioeconomic status tends to pay attention to all kinds of symptoms. Adult studies showed psychological stressors not only precipitate symptoms in FAPD, especially IBS, but also the stress severity is significantly correlated with the severity of bowel symptoms [32, 33]. The mechanisms through which stress aggravates bowel symptoms are by slowing gastric emptying, increasing colonic motility, and visceral hypersensitivity [34]. Even in FAPD, symptom-specific anxiety has shown to directly influence the pain scores [35]. In a pediatric study from China, academic performance was not a significant risk factor for FAPD, but academic stress (OR = 1.452, 95% CI: 1.105–1.906, p = 0.007) and academic performance below parental expectation (OR = 1.819, 95% CI: 1.629–2.066, $p \leq 0.001$) carry significant risk [8]. In the present study, academic stress was the major contributor to the stressor in about 22% of children, and the presence of stressor was associated with more severity of pain than the children who had no stressors.

Family history of FGIDs is commonly seen in adults with FAPD [34]. Similar findings are seen even in children. In a pediatric study of 1658 children from Greece, almost 60% of the FGID children had a family history of GI disorders [16]. In another study, 12% of the fathers and 8% of the mothers of the children with FAPD had FGIDs [36]. In the present study, 14.6% of the children had a family history of FGIDs, and children with a family history had more severe symptoms than children without a family history.

About 66 (13.9%) children with FAPD in the present study received antituberculosis therapy (ATT) before referral to our center on presumptive ground. This clearly indicates the burden of indiscriminate use of ATT among practicing pediatricians. Chest X-ray, being a diagnostic modality with low specificity (46%) still remains the only mode of diagnosis of pulmonary tuberculosis [37]. In an adult study ($n=795$) by Svadzian et al., almost 23% of the patients seen by private clinics in India were started on ATT after an abnormal X-ray [38]. In another study, of the 70 patients who developed acute liver failure secondary to ATT, 44 (62.8%) were due to empirically started ATT without appropriate microbiological diagnosis [39]. Suspicion of abdominal tuberculosis and initiating empirical ATT for the same in children with FAPD in alarmingly significant proportions need to be confirmed with more epidemiological studies.

There are several strengths of this study. This is the largest cross-sectional hospital-based study on FAPD children based on Rome IV criteria. The study discusses the clinical and social characteristics of FAPD children in a developing country, which is rarely studied. The study encounters children from a diverse population with almost equal distribution between the rural and urban populations. The limitations of the present study are mainly its retrospective design, because of which uniformity in data collection could not be established. Secondly, as the evaluation is done in the gastroenterology department, routine psychiatric assessment of the magnitude of stressors was not done. Thirdly, as the study is from a single center tertiary institution, there could be concerns with sample representation from the population, especially from the epidemiological perspectives.

6 | Conclusion

FAPDs are a commonly diagnosed cause of abdominal pain in children. FAP-NOS is the most common FAPD in children. The children with FAP-NOS are much younger than those with other subtypes of FAPD. The presence of stressors and functional disorders in family members could be associated with severe symptoms. However, it mandates more prospective studies to validate the findings.

Acknowledgments

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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