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Alimentary Tract

Functional abdominal pain disorders and patient- and parent-reported outcomes in children with inflammatory bowel disease in remission ☆,☆☆

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ABSTRACT

Background: Chronic abdominal pain occurs frequently in pediatric patients with inflammatory bowel disease (IBD) in remission.

Aims: To assess the prevalence and factors associated with Functional Abdominal Pain Disorders among IBD children in remission (IBD-FAPD).

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Methods: Patients with IBD for > 1 year, in clinical remission for ≥ 3 months were recruited from a National IBD network. IBD-FAPDs were assessed using the Rome III questionnaire criteria. Patient- or parent- reported outcomes were assessed.

Results: Among 102 included patients, 57 (56%) were boys, mean age (DS) was 15.0 (± 2.0) years and 75 (74%) had Crohn's disease. Twenty-two patients (22%) had at least one Functional Gastrointestinal Disorder among which 17 had at least one IBD-FAPD. Past severity of disease or treatments received and level of remission were not significantly associated with IBD-FAPD. Patients with IBD-FAPD reported more fatigue (peds-FACIT-F: 35.9 ± 9.8 vs. 43.0 ± 6.9, $p = 0.01$) and a lower HR-QoL (IMPACT III: 76.5 ± 9.6 vs. 81.6 ± 9.2, $p = 0.04$) than patients without FAPD, and their parents had higher levels of State and Trait anxiety than the other parents.

Conclusions: Prevalence of IBD-FAPD was 17%. IBD-FAPD was not associated with past severity of disease, but with fatigue and lower HR-QoL.

1. Introduction

The paradigms of pediatric inflammatory bowel disease (IBD) care have evolved over the last thirty years. Compared to adults, IBD in children has been described as having a more aggressive phenotype from diagnosis [1]. Progressively we have moved from treating inflammation with step-up immunomodulators and then biologics, to trying to reverse the natural history of disease, in the aim of preventing intestinal damage. The risk factors for complicated disease in pediatric IBD have been described and pediatric IBD patients can now benefit from highly effective biologics and treatment strategies early on in the course of disease [2,3].

Besides a better understanding of mechanisms of tissue damage caused by recurrent or unresolved inflammation, pediatric gastroenterologists have raised awareness on psychosocial consequences of a life-long disease in young individuals. Pediatric IBD patients suffer from increased anxiety, depression, and lower quality-of-life (QoL) than healthy controls [4,5]. These symptoms are increased in the setting of active disease [6,7].

In addition, a significant number of patients have persistent abdominal pain although they are in remission. In adults, the prevalence of these symptoms, termed "IBS-IBD" reaches up to 35% [8]. This pain seems to result from disorders in the Brain-Gut axis and in pain perception [9], although the mechanisms are not fully understood. Animal models suggested visceral hypersensitivity and anxiety persisting several weeks after chronic TNBS colitis [10].

We hypothesized that functional abdominal pain in children with IBD in remission might be a consequence of the severity of previous inflammation. The first objective of our study was to test for an association between Functional Abdominal Pain Disorder in remission of IBD (IBD-FAPD) and past characteristics of IBD. Since disorders of the Brain-Gut axis are associated with psychosocial difficulties such as depression and anxiety [11], our second objective was to evaluate correlation between psychosocial comorbidities and IBD-FAPD. Finally, to understand the patient's family context and how it could influence IBD-FAPD, we studied the association between parental anxiety and depression and IBD-FAPD.

2. Materials and methods

We conducted a multicentre cross-sectional survey in pediatric gastroenterology units affiliated to the GETAID pédiatrique (Groupe d'Etude des Affections Inflammatoires Digestives pédiatriques), a French national collaborative research network on pediatric IBD.

2.1. Population

All consecutive pediatric IBD patients seen in the outpatient clinic, inpatient ward or infusion clinic between April 2018 and March 2020 were invited to participate. The inclusion criteria were as follows: age between 9 and 18 years, a diagnosis of IBD (Crohn's disease (CD), Ulcerative colitis (UC) or IBD-Unclassified (IBD-U) confirmed according to the ESPGHAN Porto criteria [12], duration of IBD > 1 year, clinical remission defined as (all criteria mandatory): Physician's global assessment = "Remission", no nocturnal stools, no blood in stools, ≤ 3 stools per day, CRP < 5 mg/L, no ongoing steroid therapy, no recurrence of disease or optimization of treatment in the last 3 months.

Exclusion criteria were the presence of an ileostomy or colostomy, inability to understand French or refusal to participate.

2.2. Data collection

2.2.1. Patient characteristics and disease phenotype

Data collected from the chart were: disease characteristics at diagnosis of IBD (Paris classification), treatments received since diagnosis, history of steroid dependency [13] or steroid-refractory disease [14], comorbidities, most recent imaging, endoscopy, laboratory results from the last 3 months including fecal calprotectin (FC) and clinical activity indices (PCDAI, PUCAI).

Remission was categorized as follows: Clinical remission was defined as PCDAI or PUCAI < 10, biochemical remission was defined as CRP < 5 mg/L and ESR < 10 mm/h [15], endoscopic remission was defined as no ulcerations and/or CDEIS < 6 for CD and no bleeding, ulceration or erosion and/or Mayo score ≤ 1 for UC and IBD-U [16]. Histologic remission was defined as absence of neutrophils, and normal levels of plasmocytes and eosinophils in lamina propria [17].

2.2.2. Patient and parent reported outcomes

We assessed patient- and parent- reported outcomes (PRO) through validated French translations of questionnaires either on a web-based Limesurvey® module, or on paper forms.

The Fr-qPGS (Rome III Diagnostic Questionnaire for the pediatric Functional GI Disorders), was used to diagnose Functional Gastrointestinal Disorders (FGID). FGIDs were divided into the Functional Abdominal Pain Disorders (FAPD) group, comprising Functional Dyspepsia, Abdominal Migraine, Irritable Bowel Syndrome (IBS), Functional Abdominal Pain (FAP), Functional Abdominal Pain Syndrome (FAPS) and the "No pain FGIDs" group, comprising nausea and vomiting disorders (Aerophagia, Cyclic Vomiting Syndrome, Adolescent Rumination Syndrome) and defecation disorders (Functional Constipation, Nonretentive Fecal Incontinence).

The other PROs assessed were: level of fatigue using the peds-FACIT-F (pediatric Functional Assessment of Chronic Illness Therapy - Fatigue), depression using the CDI (Children's Depression Inventory), anxiety using the SCARED-R-51 (Screen for Child Anxiety Related Disorders) and Health-related quality-of-life (HR-QoL) using the IMPACT-III questionnaire.

Parents' anxiety and depression were assessed using the STAI-Y (State Trait Anxiety Inventory / Form *Y*) and the BDI (Beck's Depression Inventory) questionnaires. They were questioned on school absenteeism and alternative/complementary medicine received.

Details on the scoring of each questionnaire, and cut-offs used are provided in the Supplementary Data.

2.3. Statistical analysis

Characteristics of patients having at least one functional abdominal pain disorder ("IBD-FAPD group") according to Rome III criteria were compared to those of patients with no pain (further referred to as "No IBD-FAPD group"). Qualitative variables were compared by Pearson Chi-square or Fisher's exact test, as appropriate. Normal distribution of continuous variables was tested by Shapiro-Wilk test. Continuous variables were compared by unpaired Student t-Test or Wilcoxon non-parametric test, as appropriate. Variables associated with IBD-FAPD with a $p < 0.10$ in univariate analysis were included in a multivariable logistic regression model where the explanatory variables were baseline characteristics of IBD, treatments received, and phenotype of disease. Correlation between different psychological scores was tested by Spearman's correlation coefficient.

SAS version 9.2 (Cary, N.C., USA) was used for the analyses. A two-tailed p value < 0.05 was considered significant for all analyses with no adjustment for multiple analyses.

3. Ethical considerations

The study protocol was approved by a French ethic committee (Comité de Protection des Personnes Nord-Ouest I, N°RCB: 2017-A02420-53). Patients received a non-financial compensation for their participation (gift card). This study protocol was registered in Clinical Trials (NCT03565263).

4. Results

4.1. Description of patients

From April 2018 to March 2020, 129 patients were included from 18 study centres, among which 102 patients with complete questionnaires and CRF could be analyzed.

Among the 102 patients there were 57 boys and mean age was 15.0 ± 2.0 years (min-max 9.6–17.9). Seventy-four percent had CD, 18% had UC and 8% had IBD-U. Mean duration of IBD was 3.5 ± 2.2 years (min-max: 1.0–12.7). Treatments received since diagnosis (including current treatment) were: aminosalicylates (39%), corticosteroids (51%, none currently taking corticosteroids at inclusion in study), immunomodulators (69%), anti-TNF alpha therapy (73%), enteral nutrition (36%, only 2 patients currently receiving enteral nutrition), parenteral nutrition (6%, all were past treatments). Previous IBD-related surgeries were: perianal surgery (3%) and ileocaecal resection (2%) (Suppl Table 1). Features of complicated IBD course since diagnosis are indicated in Supplementary Table 2.

At the time of inclusion, IBD was in clinical remission for all (mean PCDAI: 1.1 ± 2.3, mean PUCAI: 0.4 ± 1.4) (Table 1). Twenty-three patients had a FC result from < 1 month: median FC was 30 [IQR 25–75: 9–137]. Thirty-one patients had an abdominal imaging within the last 6 months, among which 28 had no signs of active disease. Fifteen patients had an endoscopy within the last 6 months, among which 11 were in endoscopic remission, and 10 in histological remission.

4.2. Comparison of patients with functional abdominal pain and those without

Among the 102 patients, 22 met diagnostic criteria for at least one FGID among which 17 had diagnostic criteria for at least one FAPD (IBD-FAPD): 2 had IBS-lower location, 2 IBS-upper location, 4 abdominal migraine, 6 FAP-lower location, 2 FAP-upper location, 1 FAPS-

Lower location and 1 FAPS-upper location. Only 2 patients had an overlap between FAPD and no pain FGID (Suppl Table 3).

The baseline characteristics of patients with and without FAPD did not differ significantly (Table 1 and Suppl Table 1). There was no difference in number of hospitalizations, flares requiring steroids, treatments received or IBD complications since diagnosis between groups (Suppl Table 2).

Among the patients who had recent (< 1 month) laboratory results, or an abdominal imaging or endoscopy within the last 6 months, there was no difference between the proportion of patients in biologic, endoscopic, histologic or imaging remission between the 2 groups (Table 1). Median FC was 144 µg/g (IQR 25–75: 15–1998) in the IBD-FAPD group vs. 30 µg/g (IQR 25–75: 8,5 – 116) in the No-FAPD group ($p = 0.30$).

In the multivariable logistic regression model including all clinical and demographic variables associated with IBD-FAPD with a $p < 0.10$, none was significantly associated with IBD-FAPD.

4.3. Psychosocial comorbidities of IBD-FAPD

Patients in the IBD-FAPD group reported more fatigue, with lower total Peds FACIT-F scores than the No-FAPD group ($p = 0.01$), a lower Tiredness subscale ($p = 0.0008$) but no difference in Energy subscale (Suppl Table 3).

There was no significant association between depression and FAPD-IBD, whether using the CDI score as a continuous variable ($p = 0.11$) or the cutoffs proposed by Bang et al., ($p = 0.30$) (Fig. 1, Suppl Table 3). The anxiety SCARED R-51 score did not differ between groups nor did the subscores of anxiety. HR-QoL was significantly lower in the "IBD-FAPD" group, as reflected by a lower IMPACT-III score compared to the "No IBD-FAPD" group ($p = 0.04$). The domains of IMPACT-III that were significantly lower in the "IBD-FAPD" group were: "Bowel symptoms" ($p = 0.003$) and "Systemic symptoms" ($p = 0.008$) (Fig. 2, Suppl Table 3).

Sixty-nine percent of patients in the "IBD-FAPD" group and 50% of patients in the "No IBD-FAPD" group had been absent from school for 1 to 3 half-days per months on average over the school year. Rate of school absences was not different between groups ($p = 0.67$) (Suppl Table 3).

There was a mild but significant correlation between scores to psychological questionnaires in both groups (Table 2).

4.4. Parents of children with IBD-FAPD have higher levels of anxiety

In order to test for correlations between patient's and parent's answers, we restricted the analyses to one parent per child: if both parents had answered (only 5 patients) the mother's questionnaire was retained for analysis since anxiety and depression have been shown to be more frequent in adult women in the general population. Age and socio-professional group were not different whether their child was in the "IBD-FAPD" group or not (Data not shown). Parents of children in the "IBD-FAPD" group had a higher level of State anxiety (STAI-Y-A 43.8 ± 12.9 vs. 34.0 ± 11.2, $p = 0.006$) and Trait anxiety (STAI-Y-B 44.7 ± 9.7 vs 36.0 ± 9.5, $p = 0.003$) than

Table 1
Characteristics of patients with and without FAPD at inclusion in the study
Data expressed as *n* (%), mean ± SD for normally distributed variables and median (IQR 25–75) for non-normally distributed variables.

	IBD-FAPD (n = 17)	No IBD-FAPD (n = 85)	p
IBD sub-type (Crohn's disease,%)	12 (75%)	63 (74%)	0.72
Male (n,%)	10 (59%)	47 (55%)	0.79
Age at inclusion (yrs)	15.4 ± 1.4	14.9 ± 2.1	0.42
Duration of IBD (yrs)	2.8 ± 1.6	3.7 ± 2.3	0.14
Weight (kg)	50.9 ± 10.6	54.3 ± 15.4	0.42
Height (cm)	163.2 ± 9.1	165.6 ± 11.8	0.46
Laboratory results (< 1 month)	n = 13	n = 66	
Hemoglobin (g/dL)	14.01 ± 0.7	13.7 ± 1.3	0.39
Hematocrite (%)	41.1 ± 2.6	40.0 ± 3.9	0.50
Platelets (G/L)	231 ± 50	267 ± 69	0.23
Leucocytes (G/L)	7.6 ± 1.0	7.0 ± 2.5	0.25
ESR (mm/h)	4.8 ± 2.8	6.8 ± 5.5	0.44
CRP (mg/L)	1.0 ± 0	1.1 ± 0.8	0.27
Albumin (g/dL)	4.6 ± 0.2	4.3 ± 0.4	0.09
Fecal calprotectin (µg/g) (< 1 month)	144 (15–1998) (n = 3)	30 (8,5–116) (n = 20)	0.30
Endoscopic remission*	2 / 3	9 / 12	1.00
Histologic remission*	2 / 3	8 / 12	1.00
Imaging remission*	4/4	24/27	1.00
Current medication for IBD (*n*,%)			
Aminosalicylates	4 (24%)	16 (19%)	0.74
Immunomodulators	2 (12%)	27 (32%)	0.14
Anti-TNFα agents	11 (65%)	59 (69%)	0.78
Psychotropic treatments			
Past psychotherapy	1 (7%)	10 (12%)	1.00
Ongoing therapy	1 (7%)	5 (6%)	1.00

* Based on results of most recent endoscopy or abdominal imaging, if performed less than 6 months before inclusion.

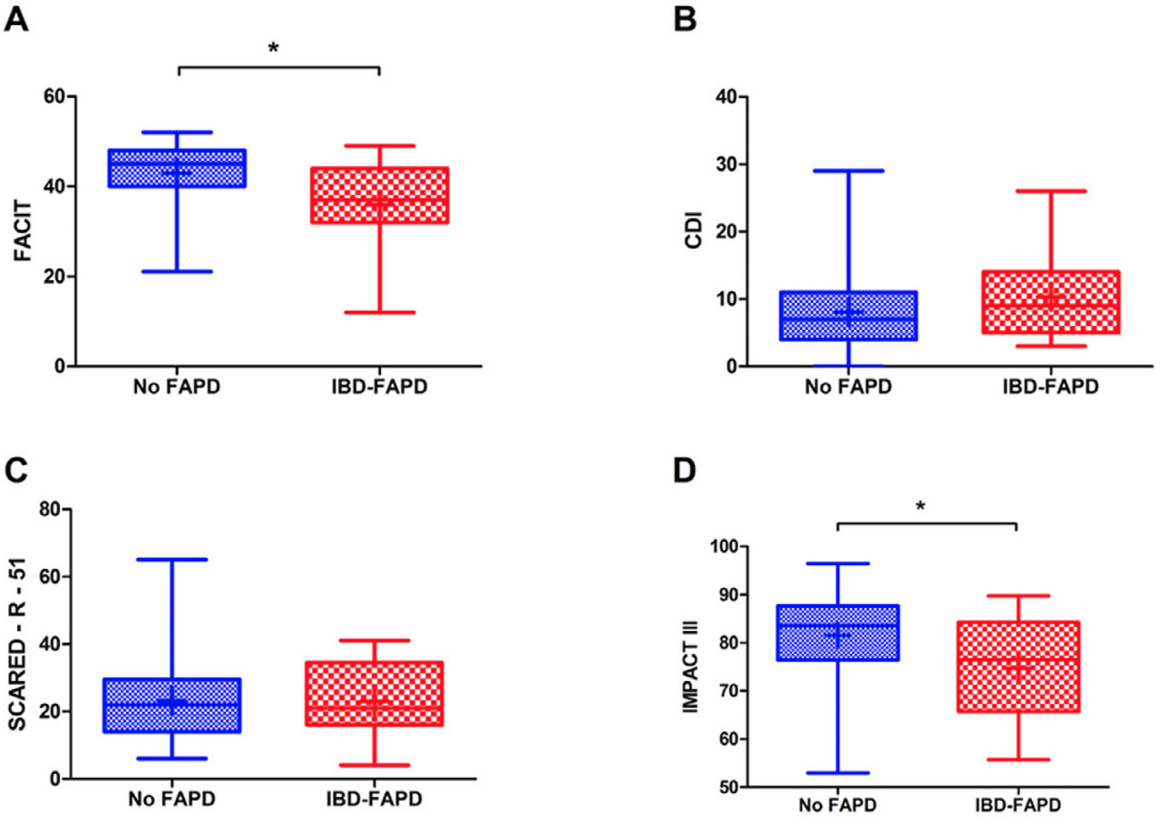

Fig. 1. Psychological comorbidities of Functional abdominal pain disorders based on self-administered questionnaires.
Panel *A*: Total Peds FACIT-F score by group (No IBD-FAPD: n = 85, IBD-FAPD: n = 17), lower scores represent higher levels of fatigue. Panel *B*: Total *CDI* score by group, higher CDI scores indicate higher levels of depression. Panel *C*: Total SCARED-R-51 score by group, higher SCARED-R-51 scores indicate higher levels of anxiety. Panel *D*: Total IMPACT III score by group, lower scores indicate lower health related quality of life.
Scores are represented as median ± IQR and whiskers indicate min and max values. * p-value < 0.05, ** p-value < 0.01.

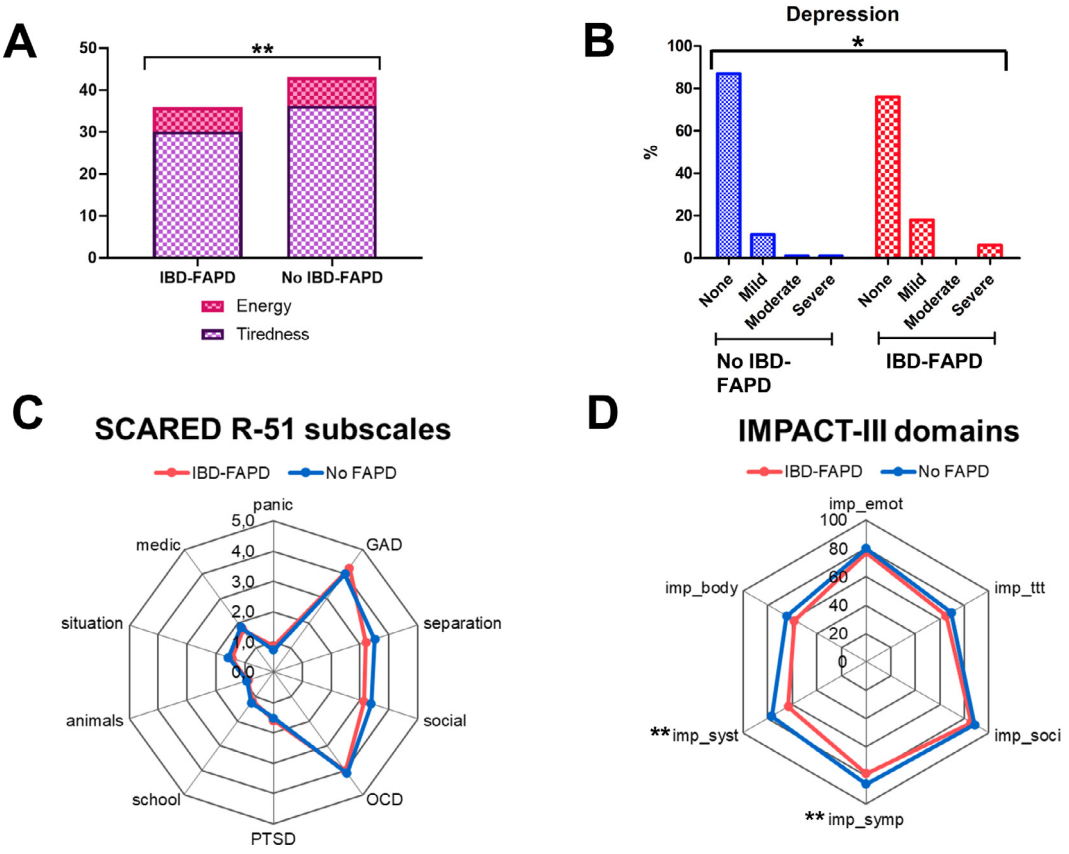

Fig. 2. Detailed answers to the psychological questionnaires, by subscore, among pediatric IBD patients in remission, comparing patients with IBD-FAPD ($n = 17$) and patients without ($n = 85$).
Panel *A*: FACIT subscores: A higher Tiredness subscore indicates less tiredness, a Lower energy subscore indicates lower energy. Panel *B*: Intensity of depression based on Bang et al. cutoffs for CDI: mild (CDI 15–19), moderate (CDI 20–24), severe (CDI ≥ 25). Panel *C*: SCARED-R-51 subscales of Anxiety Disorder: "panic": Panic Disorder, "GAD" : Generalized Anxiety Disorder, "separation": Separation Anxiety, "social" : Social Anxiety Disorder, "OCD": obsessive-compulsive disorder, "PTSD" : Post Traumatic stress disorder, "school": Significant School Avoidance, "animals" : animal phobias, "situation" : situational phobias, "medic" : phobia of medical procedures. Panel *D* : IMPACT III domains of health related quality of life : "imp_emot" : emotional functioning, "imp_ttt" : treatment/intervention, "imp_soci" : social functioning, "imp_bow" : bowel symptoms, "imp_syst" : systemic symptoms, "imp_body" : body image. * p-value < 0.05, ** p-value < 0.01.

Table 2
Correlation between psychological Patient Reported Outcomes, among patients with and without IBD-FAPD.
r= Spearman's correlation coefficient.
NS: *not significant*.

A. Patients with IBD-FAPD ($n = 17$)				
r p	IMPACT III	CDI	Peds FACIT-F	SCARED R51
IMPACT III	1	−0.64 0.006	0.65 0.004	−0.58 0.01
CDI	−0.64 0.006	1	−0.44 0.08	0.43 0.08
Peds FACIT-F	0.65 0.004	−0.44 0.08	1	−0.56 0.02
SCARED R51	−0.58 0.01	0.43 0.08	−0.56 0.02	1

B. Patients without FAPD ($n = 85$)				
r p	IMPACT III	CDI	Peds FACIT-F	SCARED R51
IMPACT III	1	−0.50 <0.0001	0.49 <0.0001	−0.43 <0.0001
CDI	−0.50 <0.0001	1	−0.45 <0.0001	0.53 <0.0001
Peds FACIT-F	0.49 <0.0001	−0.45 <0.0001	1	−0.37 0.0006
SCARED R51	−0.43 <0.0001	0.53 <0.0001	−0.37 0.0006	1

the parents of children in the "No IBD-FAPD" group (Table 3). There was no correlation between parental and child anxiety (Pearson $r = 0.19$).

BDI scores and levels of depression according to the cutoffs proposed by Pichot et al. were not significantly different between groups. There was no correlation between parental and child depression (Pearson r=−0.001).

Use of complementary medicines was marginal in the cohort, parents reported the use of the following for their child: manual therapies ($n = 7$), osteopathy ($n = 5$), shiatsu ($n = 1$), administrated surface therapies such as balms and creams ($n = 1$), mind-body therapies ($n = 6$), thermal water cure ($n = 1$), relaxation therapy and Eye Movement Desensitization and Reprocessing (EMDR) therapy ($n = 1$).

5. Discussion

In this study we have shown that functional abdominal pain in IBD in remission was not associated with past severity of the disease but resulted in fatigue and lower health-related quality-of-life.

The overlap of IBS-like symptoms in adults with IBD in clinical and biochemical remission is now well known [9,18]. However there have been only few reports in paediatrics, and none that has examined simultaneously multiple aspects of psychosocial repercussions [19–21]. In addition, most studies have focused on IBS or on FAP, but not on all FGIDs according to the Rome III classification.

Table 3
Parents' characteristics (one parent per child).
Data expressed as n (%), mean ± SD for normally distributed variables and median (IQR 25–75) for non-normally distributed variables.

	At least one IBD-FAPD (n = 13/17)	No IBD-FAPD (n = 75/85)	p
Gender of the parent answering the questionnaire (female, *n*,%)	11 (85%)	59 (84%)	1.00
Parent anxiety and depression			
STAI-Y-A	43.8 ± 12.9	34.0 ± 11.2	**0.006**
STAI-Y-B	44.7 ± 9.7	36.0 ± 9.5	**0.003**
BDI score	4.3 ± 3.8	2.4 ± 3.1	0.08
No depression (BDI ≤ 4)	6 (55%)	58 (81%)	0.06
Mild depression (BDI > 4 - ≤ 7)	2 (18%)	8 (11%)	
Moderate depression (BDI >7- ≤15)	3 (27%)	6 (8%)	
Severe depression (BDI >15)	0	0	

In this study the prevalence of FGIDs in children and adolescents with IBD in clinical remission was 22% among which IBD-FAPD represented 17% and IBS 4% of patients. These rates are similar to those observed in the general population: a meta-analysis showed a worldwide pooled prevalence of FAPD in children of 13.5% (10.5% in Europe), with IBS representing 8.8% [22].

Remission of IBD and absence of inflammation is a prerequisite for characterizing the remaining pain as being functional pain [18]. Therefore the prevalence of functional abdominal pain in IBD patients depends on the criteria chosen to define remission. In addition, criteria used to define functional pain may vary. Zimmerman et al. in a multicentre cross-sectional study in the USA showed a prevalence of functional abdominal pain of 10.3% in pediatric IBD patients in clinical remission [19]. Watson et al. reported a prevalence of pediatric IBD-FAPD according to Rome III criteria of 26%, in clinical remission [21]. Diederen et al., in a Dutch multi-center study, reported IBS-like symptoms in 16% and IBS or FAP symptoms in 22.6% of pediatric IBD patients in biochemical remission (defined as FC < 250 mg/kg) [20]. Our prevalence rates are thus in the higher range of those reported in pediatric IBD patients, tending to be closer to general population rates.

Determining the association between pain and residual inflammation remains challenging. The IBD Porto group recommends endoscopic evaluation of symptomatic patients when IBS is suspected to cause the symptoms [23].The recent ECCO/ESPGHAN pediatric CD guidelines review alternative non-invasive biomarkers [1]. Fecal calprotectin in particular is frequently used as a surrogate for mucosal healing, although there are several caveats (instability, optimal cutoff, difficulties de collect fecal samples from teenagers). With the available samples, we did not find an association between FC levels and IBD-FAPD, although we might have lacked statistical power. In addition, there were outlying values in both groups. One of the patients from the IBD-FAPD group who had a value of 1998 µg/g at inclusion, although in clinical and biological remission, was on the verge of a new phase of disease activity and would further need a treatment optimization. For all these reasons, our values of prevalence of IBD-FAPD could be expected to have been overestimated when compared to studies using FC as inclusion criteria.

Recent reports have pointed to the fact that low grade mucosal inflammation despite clinical and endoscopic remission, might result in the development of IBS-like symptoms in UC patients [24]. In the pediatric study by Diederen et al., there was no association between FC levels and IBS, among patients in clinical remission [20]. Interestingly, they found that the prevalence of IBS-like symptoms was higher (16% vs 6%) in the group of patients with a FC < 250 mg/kg than in the group of patients in clinical remission based on abbreviated PCDAI or PUCAI < 10. This suggests that using symptom-based criteria for inclusion might be more stringent than using calprotectin levels, and that functional pain in children might be independent from inflammation. The fact that the prevalence of IBS-like symptoms is not higher in pediatric IBD patients in clinical remission than in patients from population-based studies is also in favor of the hypothesis that IBS and IBD might be independent entities.

Since current inflammation was not associated with IBD-FAPD in our study, we sought for an association with previous inflammation, with the hypothesis that a severe past disease might lead to post inflammatory alterations in pain perception or visceral hypersensitivity, as it has been shown in animal models [10]. We used as a proxy for severe disease the association of steroid dependency, steroid refractory disease, requiring anti TNF therapy, complicated disease (B2, B3), perianal disease or growth retardation. However, none of these were associated with IBD-FAPD. This could mean that the patients with functional pain in this cohort might have had independent risk factors for FAPD. The fact that the prevalence of FAPD was similar to that of the general population also pleads for the fact that severe inflammation might not increase risk for FAPD. However, it must be taken into account that an important proportion of the cohort (69%) was treated by anti-TNF alpha agents, although IBD duration was relatively short (3.5 ± 2.2 years). It would be interesting to study the effect of timing of introduction of the anti-TNF agent on the eventual development of functional complications of the disease.

In our study there was a lower HR-QoL in the IBD-FAPD group. This had also been reported by Watson et al. [21]. Two domains differentiated the groups, the "bowel symptoms" and the "systemic symptoms" domains. Since the "bowel symptoms" domain comprises questions on eating, abdominal pain, diarrhea and flatulencies and the "systemic symptoms" domain comprises questions on fatigue and family's feeling toward the disease, it was expected that the patients from the IBD-FAPD group would report more impact of these symptoms on their QoL. Varni et al. showed that QoL was reduced (using PedsQL questionnaire) in children with FGID and in IBD patients, compared to controls [5]. Adding to this data we show that combination of functional abdominal pain and IBD reduces QoL compared to IBD alone. In a recent French multicentre study conducted among 218 patients with Crohn's disease, health-related QoL was independently associated with clinical remission [7].

Depression and anxiety are frequently reported in children and adolescents with IBD [4] as well as in children without IBD but suffering from functional abdominal pain [22]. A recent meta-analysis showed a pooled prevalence of anxiety symptoms of 16.4% and depressive symptoms of 15% in pediatric IBD [4]. In the study by Zimmerman et al., 55% of children with functional abdominal pain and IBD in remission had depression, compared to 30% in children with no pain and a PCDAI ≤ 10 (p = 0.03)(19). Using the same score and cutoff, we did not find a significant increase of depressive symptoms in the FAPD-IBD group. However, since chronic pain in children in general has been shown to be associated with depression,

this should be screened for in general practice and referred accordingly [25].

We were expecting to find an association between anxiety and FAPD. Although there was no increase in anxiety scores in children with IBD-FAPD, the parents of children from the IBD-FAPD group had significantly more anxiety than the other parents. We can speculate that although the children were not exceedingly anxious, the fact that their parents had anxiety might have amplified their perception of pain. One of the hallmarks of care of pediatric patients with functional abdominal pain is reassurance by the caregivers [26]. The alternative explanation would be that their child's disease caused anxiety in the parent, and that anxiety persisted because of persisting symptoms.

Finally we noted that children in the IBD-FAPD group had significantly more fatigue than the "No IBD-FAPD" group, although the overall scores using the FACIT-F 13-item questionnaire were in the same range as reported in adult IBD patients [27]. In the adult study, patients with inactive disease had a mean FACIT-F score of 40.2 in CD and 42.2 in UC [27]. Fatigue is a symptom frequently reported in adults with IBD but data is lacking in pediatric IBD [28].

All of the psychological aspects were correlated (QoL, fatigue, depression and anxiety), which shows a complex interplay of these factors and the necessity to take each of them into account. Several parents reported that their child had received complementary medicines. To date there are no recommendations concerning optimal management of IBD-FAPD in children, although there have been reports of successful implementation of mind-body interventions [29].

Considering reproducibility of our results, we recognize that the patients who accepted to participate in the study might reflect a milder course of disease, although their baseline characteristics were comparable to data from population based registries [1]. Indeed, the majority had not been hospitalized (apart from initial hospitalization for diagnostic work-up) and had less than one flare requiring steroids since diagnosis. Another clue is that 72% of patients were currently on anti-TNF alpha treatment, which is higher than population based pediatric studies. There might have been an inclusion bias based on mode of recruitment of patients (in the infusion clinic rather than outpatient clinic?). Nonetheless we seem to have captured an interesting group of patients who as a whole are doing well despite their IBD and have lower anxiety and fatigue scores than comparable studies. In the absence of IBD complications, it seems possible that the anti-TNF therapy was initiated early in the course of disease, due to predictive factors of poor outcome according to ECCO/ESPGHAN pediatric recommendations and not after complications had occurred [2]. Whether this therapeutic strategy could equally have beneficial effects on Brain-Gut axis and psychological outcomes should be further evaluated.

6. Conclusion

In conclusion, we have shown that the prevalence of IBD-FAPD in pediatric patients in clinical and biochemical remission is similar to that of the general population. IBD-FAPD was associated with fatigue, lower QoL and parental anxiety, but not with child anxiety or depression. Although past severity of disease did not differ between groups, the patients in the study had a high rate of current biologic medications and had few flares since the diagnosis of IBD. We speculate that beginning early in the course of disease highly efficacious medications and obtaining rapid remission might have prevented disturbances of the brain-gut axis.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.05.034.

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