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INFOGRAPHIC

Fatigue and Physical Activity Patterns in Children With Inflammatory Bowel Disease

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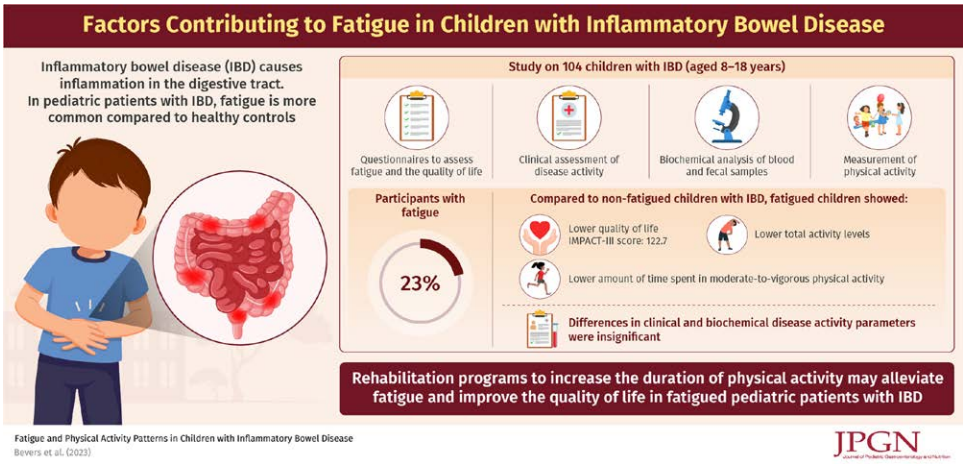

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What Is Known

- Fatigue is a common and invalidating symptom in children with inflammatory bowel disease.
- Treatment of anemia and/or disease activity does not always solve the problem.

What Is New

- Biological parameters did not discriminate fatigued from non-fatigued children.
- Fatigued children spent less time in the "moderate-to-vigorous activity" category.
- This finding could be used in future interventions to combat fatigue.

ABSTRACT

Objectives: Fatigue is a common symptom in children with inflammatory bowel disease (IBD). Diagnostic tests to evaluate biological causes of fatigue commonly include markers of inflammation and hemoglobin (Hb), yet functional parameters have been inadequately studied in pediatric IBD. In this study, we compared fatigued and non-fatigued children with IBD from both a biological and functional point of view.

Methods: A cross-sectional study of 104 pediatric IBD patients with mild to moderately active IBD was conducted. Fatigued children were defined as those with a Pediatric Quality of Life Inventory Multidimensional Fatigue Scale *z* score <−2.0. Non-fatigued children had a *z* score ≥−2.0. Disease-specific quality of life (measured with IMPACT-III score), C-reactive protein (CRP), fecal calprotectin (FC), hemoglobin *z* score (Hb *z* score), and physical activity tests including 6-minute walking distance *z* score (6MWD *z* score) and triaxial accelerometry (TA) were evaluated.

Results: Fatigued children (n = 24) had a significant lower IMPACT-III score than non-fatigued children (n = 80). Hb *z* scores, CRP, FC, and 6MWD *z* scores were not significantly different between groups. TA was performed in 71 patients. Wear time validation requirements were met in only 31 patients. Fatigued patients spent significant shorter median time in moderate-to-vigorous activity than non-fatigued patients (18.3 vs 37.3 minutes per day, $P = 0.008$).

Conclusion: Biological parameters did not discriminate fatigued from non-fatigued patients. TA possibly distinguishes fatigued from non-fatigued patients; the potential association may provide a target for interventions to combat fatigue and improve quality of life.

Key Words: accelerometry, children, fatigue, IBD

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The inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn disease (CD), are chronic inflammatory disorders of the gastrointestinal tract characterized by episodes of inflammation and remission. Children living with IBD often experience a wide range of symptoms such as diarrhea, abdominal pain, weight loss, rectal bleeding, and fatigue (1). Fatigue is more frequent and more severe in patients with IBD than in the general population and is present during active inflammation as well as during disease remission. It can therefore be an additional hindrance for children to participate in daily activities such as hobbies and school (2).

Little is known about the causes of fatigue in pediatric IBD, hampering its management. Most studies comparing fatigued and non-fatigued patients have been confined to biological factors (such as disease activity and anemia) (3,4). Information about functional factors such as physical activity (PA) and psychosocial factors in children and adolescents with IBD are scarce.

To improve our understanding of fatigue, we conducted a cross-sectional study to assess both biological and functional factors in children and adolescents with mild to moderately active IBD.

MATERIALS AND METHODS

Study Population

This cross-sectional study was nested in the POPEYE study, a recently reported randomized, multicenter controlled trial comparing the effects of oral versus intravenous iron on physical fitness and hemoglobin (Hb) (4). Recruitment took place from June 2015 until May 2019 at the outpatient clinics of 5 tertiary care centers and 6 large teaching hospitals in the Netherlands and Belgium.

Children were eligible for inclusion in this trial when they had sufficient knowledge of the Dutch language to complete questionnaires, had IBD according to the revised Porto criteria (5) and were aged between 8 and 18 years. Unlike in the POPEYE trial, children could participate in this nested trial when they had an Hb in the normal range. Exclusion criteria were not completing the Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale (6) or severe disease activity [Pediatric Ulcerative Colitis Activity Index (PUCAI) score > 65 or a Pediatric Crohn Disease Activity Index (PCDAI) > 30] (7,8). The latter exclusion criteria originated from the POPEYE trial, as iron therapy was believed to exacerbate ongoing active inflammation.

Data Collection

Patients completed questionnaires to evaluate fatigue and quality of life (see section *2.4.2*). Disease activity was assessed clinically with PCDAI/PUCAI scores and biochemically with blood and fecal samples to analyze Hb, CRP, erythrocyte sedimentation rate (ESR), and FC. PA was assessed using the 6-minute walking test (6MWT) and a triaxial accelerometer (see section *2.4.3*). These measurements were all conducted in a time span of 2 weeks before until 2 weeks after completion of the questionnaires.

Ethical Aspects

The study was registered in the Netherlands Trial Registry [NTR4487] before recruitment of the first participant. The trial was conducted according to the principle of the Declaration of Helsinki [64th version, October 2013] and in accordance with the Dutch Medical Research Involving Human Subjects Act. The Medical Ethical Committee approved the study protocol [NL42995.096.12]. Secondary approval was obtained from all participating centers. All parents or legal guardians and participants aged 12–18 years provided informed consent.

Definitions

Active Disease

A composite score was used to distinguish children with significant inflammation from those with inactive disease. For patients with CD, the Mucosal Inflammation Non-Invasive index was used (9). A score of 8 or more was considered a proxy for active mucosal inflammation. In patients with UC, a PUCAI score ≥10 in combination with a FC concentration ≥250 μg/g feces was considered a proxy for active mucosal inflammation.

Fatigue and Quality of Life

We used the 18-item PedsQL Multidimensional Fatigue Scale to measure fatigue in pediatric patients. It comprises the General

Fatigue Scale (6 items), Sleep/Rest Fatigue Scale (6 items), and Cognitive Fatigue Scale (6 items). Participants completed the Dutch version for children (8–12 years) or for adolescents (13–18 years). All items were scored on a 5-point Likert scale with a recall period of 1 month.

Each item was then reverse-scored and rescaled to 0–100, so that higher scores indicate fewer symptoms of fatigue.

PedsQL Multidimensional Fatigue Scale scores were expressed as *z* scores derived from published normative data. IBD patients were defined as fatigued when the PedsQL score was more than 2 standard deviations below the age-specific mean (*z* score <−2) (6).

Quality of life was measured using the IMPACT-III questionnaire. This is a disease-specific questionnaire, that comprises 35 items in 6 domains: IBD-related symptoms (7 items), systemic symptoms (3 items), emotional functioning (7 items), social functioning (12 items), body image (3 items), and treatment/intervention-related concerns (3 items) (10). Each item is scored on a 5-point Likert scale, coded from 1 to 5 points. The maximum score is 175, higher scores indicate better quality-of-life. The Impact-III (NL) is a translated and modified version of the original Canadian Impact questionnaire and has been validated for use in children of 8 years and older with a recall period of 2 weeks (10).

Functional Parameters

The 6MWT was used to assess exercise capacity. The test is expressed as the distance a person can walk at a constant, uninterrupted pace in 6 minutes. Age-based reference values have been published and allow to convert individual walking distances into *z* scores (11–13).

PA was measured using a triaxial accelerometer (ActiGraph wGT3X-BT). Participants were asked to wear the accelerometer attached via a waistband on the right hip for 7 consecutive days during waking hours, except during water activities and intensive contact sports. Accelerometry data were downloaded using 10-second epoch lengths and analyzed with ActiLife software (ActiGraph, Corp, USA). Valid wear time was defined as a minimum of 4 days including 1 weekend day, consisting of at least 480 minutes per day of recording. Derived data was expressed as mean counts per minute (cpm). To establish time spent in different intensity categories, the cut-off points developed by Evenson et al (14) were used: sedentary time was 0 to 99 cpm, light intensity PA (LPA) was 100 to 2295 cpm, and moderate-to-vigorous physical activity (MVPA) was 2296 cpm or more.

The World Health Organization (WHO) recommends that children and adolescents undertake ≥60 minutes per day of MVPA as it provides health benefits (15).

Anemia

Anemia was defined as Hb > 2 standard deviations (*z*) below the mean of the WHO reference values (16).

Statistical Analyses

Descriptive statistics are presented as mean (SD) or median (IQR, ie, the 25th and 75th percentile) depending on normality checked visually with histograms. Differences were analyzed between fatigued and non-fatigued children, using independent samples *t* test (assuming a normal distribution in each group) or Mann-Whitney *U* test for numerical variables and Chi-square or Fisher exact tests for categorical variables. Continuous variables were checked for normality using histograms and normal P-P plots with tests. Distributions of PedsQL and 6MWD *z* scores among IBD patients were compared with the healthy reference population using the Kolmogorov Smirnov test. Univariable and multivariable logistic regression analyses were performed to identify risk factors for fatigue.

RESULTS

Study Population

A total of 130 patients were eligible; 26 patients were excluded as 20 did not complete the PedsQL Multidimensional Fatigue Scale at inclusion, 4 had severe disease, and 2 patients were unable to perform the 6MWT (see Figure 1, Supplemental Digital Content 1, *http://links.lww.com/MPG/D241*).

Prevalence of Fatigue

Twenty-four of 104 participants (23%) were fatigued. Table 1 shows that age, body mass index, disease location, and current treatment were not significantly different between fatigued and non-fatigued patients nor were biochemical parameters such as Hb *z* score, CRP, ESR, and calprotectin. Fatigued children had a significantly lower IMPACT-III score than the non-fatigued (122.7 vs 146.1, $P = 0.00$).

Fatigue and Functional Parameters

Mean 6MWD *z* scores between fatigued and non-fatigued patients were not significantly different (resp. 1.8 *z* score vs −1.6 *z* score).

Triaxial accelerometry (TA) was performed in 71 patients; 19 files were lost caused by technical problems. From the remaining 52 files, wear time validation requirements were met in 34 patients. Three patients did not complete the PedsQL; 31 patients were included in the analyses. The characteristics for this subgroup were comparable to those of the total population (see Table 1).

Patients spent most of their time in sedentary behavior which was not significantly different for fatigued versus non-fatigued patients (resp. 87% vs 82%, $P = 0.193$).

The time spent in different PA levels between fatigued and non-fatigued patients is presented in Table 2. There was a significant difference in time spent in MVPA per day between non-fatigued and fatigued patients (resp. 37 vs 18 min/day, $P = 0.008$). The percentage of participants fulfilling the recommended 60 min MVPA per day was overall 16% (5/31).

Factors Associated with the Presence and Severity of Fatigue

Univariable logistic regression analysis showed that female sex ($P = 0.01$), PCDAI/PUCAI score ($P = 0.035$), and IMPACT III score ($P \leq 0.001$) were associated with fatigue. Combined clinical and biochemical disease activity parameters ($P = 0.738$), 6MWD *z* score ($P = 0.64$), and Hb *z* score ($P = 0.794$) were not univariably associated with fatigue.

On multivariable logistic regression, after adjustment for other variables, IMPACT-III score was the only factor independently associated with fatigue (Table 3). When we repeated these analyses for every sub-domain in the IMPACT-score, a significant difference remained between fatigued and non-fatigued patients (Table 4). TA data could not be included in this analysis because of a high number of patients with missing values.

On sensitivity analysis, in which the definition of fatigue was changed to PedsQL *z* score <−1, only IMPACT-III score was a significant risk factor ($P < 0.001$) (see Table 1, Supplemental Digital Content 1, *http://links.lww.com/MPG/D240*).

DISCUSSION

Key Results

A quarter of our study cohort with mild to moderately active IBD scored themselves as fatigued based on the PedsQL Multidimensional Fatigue Scale. They could not be distinguished from their non-fatigued peers by Hb *z* scores, combined clinical and

TABLE 1. Characteristics of fatigued versus non-fatigued pediatric inflammatory bowel disease (IBD) patients of the main cohort (N = 104) and for the subgroup with accelerometry data (N = 31)

	Total (N = 104) (main cohort)	Fatigued (N = 24)	Non-fatigued (N = 80)	*P* value	Total (N = 31) (subgroup with accelerometry data)	Fatigued (N = 4)	Non-fatigued (N = 27)	*P* value
Demographics								
Mean age in years (SD)	14.0 (2.5)	14.3 (2.5)	14.0 (2.5)	0.522	13.5 (2.7)	13.5 (1.7)	13.6 (3.0)	0.971
Mean BMI in kg/m^2 (SD)	19.2 (3.3)	20.8 (4.1)	18.8 (2.9)	0.036	18.7 (2.5)	18.3 (2.1)	18.8 (2.6)	0.700
Females, n (%)	49 (47.1)	17 (70.8)	32 (40.0)	0.008	11 (35.5)	1 (25)	10 (37)	0.639
IBD phenotype								
Crohn disease, n (%)	78 (75)	19 (79.2)	59 (73.8)	0.428	21 (67)	4 (100)	19 (70.4)	0.335
Disease location according to Paris Classification, n (%)				0.85				0.861
L1: terminal ileal	11 (13.9)	2 (10.5)	9 (15.0)		4 (12.9)	1 (25)	3 (15.8)	
L2: colon	26 (32.9)	7 (36.8)	19 (31.7)		8 (25.8)	1 (25)	7 (36.8)	
L3: ileocolonic	42 (53.2)	10 (52.6)	32 (53.3)		11 (35.5)	2 (50)	9 (47.4)	
Ulcerative colitis, n (%)	26 (25)	5 (20.8)	21 (20.3)	0.428	10 (23)	0 (0)	8 (29.6)	0.335
Disease location according to Paris Classification, n (%)				0.551				–
E1: ulcerative proctitis	2 (8.3)	–	2 (10.5)				1 (12.5)	
E2: left-sided UC (distal tot splenic flexure)	2 (8.3)	–	2 (10.5)				2 (25)	
E3: extensive (distal to hepatic flexure)	2 (8.3)	–	2 (10.5)				1 (12.5)	
E4: pancolitis (proximal to hepatic flexure)	18 (75)	5 (100)	13 (68.4)				4 (50)	
Current medical therapy, n (%)								
Oral corticosteroid	7 (6.7)	1 (4.2)	6 (7.5)	0.568	6 (19.4)	0 (0)	6 (22.2)	0.849
Aminosalicylates	23 (22.1)	3 (12.5)	20 (25.0)	0.196	10 (32.3)	1 (25)	9 (33.3)	0.739
TNF-alpha blockers	31 (29.8)	6 (25)	25 (31.3)	0.557	9 (29)	1 (25)	8 (29.3)	0.849
Inflammatory parameters								
Active disease (combined clinical and biochemical parameters), n (%)	47 (45.2)	10 (43.5)	37 (47.4)	0.738	19 (61.3)	2 (50)	17 (63)	0.945
Median PCDAI (IQR)	7.5 (0–15)	11 (7–16)	6 (0–15)	0.116	10 (4–16)	15 (14–21)	7.5 (1–16)	0.146
Median PUCAI (IQR)	5.0 (0–16)	10 (4–25)	3 (0–10)	0.196	0 (0–7.5)	–	0 (0–10)	0.727
Biochemical parameters								
Mean Hb *z* score	−1.7 (1.7)	−1.8 (1.2)	−1.7 (1.8)	0.797	−2.1 (1.9)	−2 (1.4)	−2.2 (2.0)	0.841
Median ESR in mm/h (IQR)	12 (4–21)	12 (5–20)	12 (4–23)	0.924	13 (4–25)	11 (5.5–17)	13 (4–26)	0.513
Median CRP in mg/L (IQR)	2.0 (1.0–7.4)	1.2 (0.8–2.5)	2.2 (1.0–12.0)	0.179	3 (1.2–15.5)	1 (0.6–1.5)	6 (1.7–19.5)	0.064
Median calprotectin in µg/g (IQR)	328 (42–1051)	322 (29–1514)	328 (48–876)	0.992	261 (66–1062)	129.5 (2–1447)	444 (81–1062)	0.444
Anemia, n (%)	44 (42.3)	13 (54.2)	31 (38.8)	0.180	19 (61.3)	2 (50)	17 (63)	0.619
Functional parameters								
Mean IMPACT III score (SD)	141 (23)	123 (25)	146 (19)	<0.001	141 (19)	121 (9)	143 (19)	0.020
Mean 6MWD *z* score (SD)	−1.6 (1.4)	−1.8 (1.6)	−1.6 (1.4)	0.730	−1.6 (1.3)	−0.8 (1.6)	−1.7 (1.2)	0.184

6MWD = 6-minute walking distance; BMI = body mass index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IQR = interquartile range; PCDAI = Pediatric Crohn Disease Activity Index; PUCAI = Pediatric Ulcerative Colitis Activity Index; SD = standard deviation.

TABLE 2. Measurements of physical activity by triaxial accelerometry in fatigued and non-fatigued pediatric inflammatory bowel disease (IBD) patients

Characteristic	Total (n = 31)	Fatigued (n= 4)	Non-fatigued (n = 27)	*P* value
Wear time accelerometer, min (IQR)	9277 (7947–9646)	9946 (6183–10,443)	9119 (7947–9591)	0.237
Overall physical activity, cpm (IQR)	402 (313–526)	295 (242–423)	414 (323–531)	0.107
Median time spent in SB, % (IQR)	83 (80–86)	87 (80–88)	82 (80–86)	0.193
Median time spent in SB, min/day (IQR)	970 (904–1059)	1092 (753–1134)	969 (904–1034)	0.237
Time spent in LPA, % (IQR)	14 (12–16)	11 (11–18)	14 (13–16)	0.408
Median time spent in LPA, min/day (IQR)	155 (131–184)	152 (129–168)	163 (131–196)	0.441
Time spent in MVPA, % (IQR)	3 (2–4)	2 (1–2)	3 (2–4)	0.012
Median time spent in MVPA, min/day (IQR)	33 (20–45)	18 (13–20)	37 (25–48)	0.008

cpm, counts per minute; IQR = interquartile range; LPA = light physical activity; MVPA = moderate-to-vigorous physical activity; SB = sedentary behavior.

TABLE 3. Odds ratios and 95% confidence intervals for factors associated with fatigue in univariable and multivariable logistic regression analyses

Factors	Odds ratio	95% CI	*P* value
Univariable			
Female sex	3.64	1.36–9.78	0.01
PUCAI/PCDAI	1.05	1.00–1.11	0.035
IMPACT-III score	0.95	0.92–0.97	< 0.001
Hb *z* score	0.96	0.73–1.27	0.794
Disease activity	0.85	0.33–2.18	0.738
6MWD *z* score	0.92	0.66–1.29	0.64
Multivariable			
Female sex	2.76	0.90–8.46	0.075
PUCAI/PCDAI score	1.05	1.00–1.12	0.071
IMPACT-III score	0.95	0.92–0.98	< 0.001

6MWD = 6-minute walking distance; CI = confidence interval; PCDAI = Pediatric Crohn Disease Activity Index; PUCAI = Pediatric Ulcerative Colitis Activity Index.

TABLE 4. Odds ratios and 95% confidence intervals of the various domains of the IMPACT-III questionnaire in relation to fatigue

Factors	Odds ratio	95% CI	*p*-value
Univariable			
IBD related symptoms	0.97	0.95–0.99	0.002
Systemic symptoms	0.96	0.95–0.98	<0.001
Emotional functioning	0.97	0.95–0.99	<0.001
Social functioning	0.96	0.93–0.98	<0.001
Body image	0.98	0.96–0.99	0.006
Treatment related concerns	0.98	0.96–1.00	0.008

CI = confidence interval; IBD= inflammatory bowel disease.

biochemical disease activity parameters nor by 6MWD *z* score. The only distinguishing parameters were disease-related quality of life, which was significantly lower in fatigued children, and PA measured by TA. Total activity in counts per minute was lower compared to the general population (17) and median time spent in MVPA was shorter for fatigued versus non-fatigued children.

Comparison With Other Studies

The mean total *z* score of the Child Self Report PedsQL Multidimensional Fatigue Scale in our study cohort was comparable to a similarly aged American cohort of IBD patients described by Marcus et al (18) (resp. −1 vs −0.7 [*Z*]). They observed no association between disease activity and fatigue. Recently published adult studies on fatigue and IBD showed a similar lack of association (19,20).

Vanhelst et al (21) observed that children with IBD had similar activity patterns as compared to healthy controls, except male IBD patients who had reduced MVPA. In our study cohort the self-reported fatigued children also had reduced MVPA. They used the same accelerometer to measure PA in children with IBD, but applied the Romanzini instead of Evenson cut-offs (22) to classify PA (sedentary behavior, LPA, MVPA) which complicates

comparison of findings. In our study, the Evenson cut-offs were chosen as they exhibit superior classification accuracy and are therefore recommended to measure PA in children aged between 5 and 15 years (23).

In a study from Vogelaar et al (24), physical fitness and PA of fatigued and non-fatigued IBD patients were compared. Although the participants were adults and classification of fatigued versus non-fatigued was based on the Checklist Individual Strength-Fatigue score, they also found a non-significant difference in 6MWD and did find a difference in the intensity of PA in the fatigued- compared to the non-fatigued patients (effect size: 1.02; $P = 0.037$). This could point in the direction that especially intensity of PA is different between fatigued and non-fatigued patients, clarifying why 6MWD was not differentiating between both groups.

Participation in MVPA is important as it has major health benefits. In adults and children with metabolic syndrome, for example, there appears to be a dose-response association between MVPA and mortality (25). Nowadays, various national health councils advice children and adolescents to engage in MVPA for at least an hour per day (15,26). Only a small proportion of the participants in our study and in the study by Vanhelst reached this target (resp. 16% and 32%).

Quality of life was measured with the disease-specific IMPACT-questionnaire and was significantly lower in fatigued patients compared to non-fatigued patients. The questions about fatigue are part of the "systemic symptoms" domain of the IMPACT-questionnaire ("How much energy did you have during the last 2 weeks? How tired have you felt in the last 2 weeks?"). We repeated our analyses for every sub-domain of the IMPACT-questionnaire (Table 4), but the differences between fatigued and non-fatigued patients remained significant. A limitation of our study is the omission of the parent proxy report which can be offered next to the Child Self Report PedsQL Multidimensional Fatigue Scale. Inclusion of the parent proxy report could possibly have resulted in higher proportions of fatigued children, as parents tend to observe symptoms of tiredness sooner than the children themselves.

CONCLUSIONS

This study shows that fatigue is a common complaint in children and adolescents with IBD irrespective of combined clinical and biochemical parameters of disease activity and anemia. Patients with fatigue experience a lower quality-of-life.

Fatigued children spent shorter time in MVPA compared to non-fatigued children. We advise future researchers to use the Evenson cut-offs to interpret accelerometry data. Rehabilitation programs aiming at increasing time spent in MVPA may be successful in improving physical fitness and reducing fatigue in children with IBD.

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