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Fatigue and physical activity patterns in children with Inflammatory Bowel Disease

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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 haemoglobin (Hb), yet functional parameters have been inadequately studied in paediatric 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 paediatric IBD patients with mild to moderately active IBD was conducted. Fatigued children were defined as those with a Pediatric Quality of Life Inventory (PedsQL^{TM}) 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), faecal calprotectin (FC), haemoglobin 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 6 MWD 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 versus 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.

Keywords: IBD, children, accelerometry, fatigue

What is known:

- Fatigue is a common and invalidating symptom in children with inflammatory bowel disease
- Treatment of anaemia 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

Abbreviations:

cpm	counts per minute
CRP	C-Reactive Protein
ESR	Erythrocyte Sedimentation Rate
Hb	Haemoglobin
FC	Faecal Calprotectin
IBD	Inflammatory Bowel Disease
IQR	Interquartile Range
LPA	Light intensity Physical Activity
MVPA	Moderate-to-Vigorous Physical Activity
PA	Physical Activity
PUCAI	Paediatric Ulcerative Colitis Activity Index
PCDAI	Paediatric Crohn's Disease Activity Index
PedsQL	Pediatric Quality of Life Inventory Multidimensional Fatigue Scale
QoL	Quality of Life
SB	Sedentary Behaviour
TA	Triaxial Accelerometry
QoL	Quality of Life
6MWD	6-Minute Walking Distance
6MWT	6-Minute Walking Test

Introduction

The inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's 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 diarrhoea, 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 (2) 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. (2-4)

Little is known about the causes of fatigue in paediatric IBD, hampering its management. Most studies comparing fatigued and non-fatigued patients have been confined to biological factors (such as disease activity and anaemia).(3) 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 haemoglobin. (4) Recruitment took place from June 2015 until May 2019 at the outpatient clinics of five tertiary care centers and six 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 8-18 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 PedsQL™ Multidimensional Fatigue Scale (6) or severe disease activity (Paediatric Ulcerative Colitis Activity Index (PUCAI) score > 65 or a Paediatric Crohn's 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 faecal samples to analyse Hb, CRP, Erythrocyte Sedimentation Rate (ESR) and FC. Physical activity 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 two weeks before until two 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 Crohn's disease, the Mucosal Inflammation Non-Invasive (MINI) index was used. (9) A score of 8 or more was considered a proxy for active mucosal inflammation. In patients with ulcerative colitis, a PUCAI-score ≥ 10 in combination with a FC concentration ≥ 250 μg/g faeces 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 paediatric 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 (8-12y) or for adolescents (13-18y). 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). (12) 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 six-minute walk test 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)

Physical activity (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 seven consecutive days during waking hours, except during water activities and intensive contact sports. Accelerometry data were downloaded using 10-second epoch lengths and analysed with Actilife software (Actigraph, Corp, USA). Valid wear time was defined as a minimum of 4 days including one weekend day, consisting of at least 480 min 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. were used: sedentary time (ST) 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. (14)

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

Anaemia

Anaemia 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, i.e the 25th and 75th percentile) depending on normality checked visually with histograms. Differences were analysed 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's 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 6 MWT (see Supplemental Digital Content Figure S1, http://links.lww.com/MPG/D241).

Prevalence of fatigue

Twenty-four of 104 participants (23%) were fatigued. Table 1 shows that age, BMI, 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, 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 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 sub-group were comparable to those of the total population (see Table 1).

Patients spent most of their time in sedentary behaviour which was not significant different for fatigued versus non-fatigued patients (resp. 87 versus 82%, p= 0.193).

The time spent in different physical activity 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 min/day 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= <0.001) were associated with fatigue. Combined clinical and biochemical disease activity parameters (p= 0.738), 6 MWD 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). Triaxial accelerometry 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 Supplemental Digital Content, Table S1, 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 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 physical activity measured by triaxial accelerometry. 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 and colleagues (resp. -1 versus -0.7 [Z]). (18) 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 physical activity. In our study cohort the self-reported fatigued children also had reduced MVPA physical activity. They used the same accelerometer to measure physical activity in children with IBD, but applied the Romanzini

instead of Evenson's cut-offs (22) to classify physical activity (SB, LPA, MVPA) which complicates comparison of findings. In our study, the Evenson's cut-offs were chosen as they exhibit superior classification accuracy and are therefore recommended to measure physical activity in children aged between 5 and 15 years. (23)

In a study from Vogelaar et al (24), physical fitness and physical activity 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 physical activity 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 physical activity 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.

Conclusion

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 anaemia. 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 programmes 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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Figure legends:

Figure S1. Study flow chart

Table 1: Characteristics of fatigued versus non-fatigued paediatric inflammatory bowel disease (IBD) patients of the main cohort (N=104) and for the sub-group with accelerometry data (N=31).

	Total (N=104) (main cohort)	**Fatigued (N= 24)**	**Non-fatigued (N= 80)**	*p*-value	**Total (N= 31) (sub-group 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's 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 (%)	11 (13.9)	2 (10.5)	9 (15.0)	0.850	4 (12.9)	1 (25)	3 (15.8)	0.861
	26 (32.9)	7 (36.8)	19 (31.7)	0.428	8 (25.8)	1 (25)	7 (36.8)	0.335
	42 (53.2)	10 (52.6)	32 (53.3)	0.551	11 (35.5)	2 (50)	9 (47.4)	
L1: terminal ileal	26 (25)	5 (20.8)	21 (20.3)		10 (23)			-
L2: colon	2 (8.3)	-	2 (10.5)			0 (0)	8 (29.6)	
L3: ileocolonic	2 (8.3)	-	2 (10.5)					
Ulcerative colitis, n (%)	2 (8.3)	-	2 (10.5)				1 (12.5)	
Disease location according to Paris Classification, n (%)	18 (75)	5 (100)	13 (68.4)				2 (25)	
							1 (12.5)	
							4 (50)	
E1: ulcerative proctitis								
E2: left-sided UC (distal tot splenic flexure)								
E3: extensive (distal to hepatic flexure)								
E4: pancolitis (proximal to hepatic flexure)								
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/hour (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
Anaemia, 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

Abbreviations: CRP C-Reactive Protein, ESR Erythrocyte Sedimentation Rate, IQR Interquartile Range, PUCAI Paediatric Ulcerative Colitis Activity Index, PCDAI Paediatric Crohn's Disease Activity Index, SD standard deviation, 6MWD 6- minute walking distance

Table 2. Measurements of physical activity by triaxial accelerometery in fatigued and non-fatigued paediatric inflammatory bowel disease (IBD) patients.

Characteristic	**Total (n=31)**	**Fatigued (n= 4)**	**Non-fatigued (n= 27)**	*p*-value
Wear time accelerometer in minutes (IQR)	9277 (7947 – 9646)	9946 (6183 – 10443)	9119 (7947 – 9591)	0.237
Overall physical activity in cpm (IQR)	402 (313 – 526)	295 (242-423)	414 (323-531)	0.107
Median time spent in SB in percentage (IQR)	83 (80 – 86)	87 (80 - 88)	82 (80- 86)	0.193
Median time spent in SB in minutes/day (IQR)	970 (904 – 1059)	1092 (753 – 1134)	969 (904-1034)	0.237
Time spent in LPA in percentage (IQR)	14 (12 – 16)	11 (11-18)	14 (13-16)	0.408
Median time spent in LPA in minutes/day (IQR)	155 (131-184)	152 (129-168)	163 (131-196)	0.441
Time spent in MVPA in percentage (IQR)	3 (2 – 4)	2 (1-2)	3 (2 -4)	0.012
Median time spent in MVPA in minutes/day (IQR)	33 (20-45)	18(13-20)	37 (25-48)	0.008

Abbreviations: IQR Interquartile Range, cpm counts per minute, SB sedentary behaviour, LPA light physical activity, MVPA moderate-to-vigorous physical activity

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

Abbreviations: CRP C-Reactive Protein, PUCAI Paediatric Ulcerative Colitis Activity Index, PCDAI Paediatric Crohn's Disease Activity Index, SD standard deviation, 6MWD 6- minute walking distance

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