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ORIGINAL RESEARCH

Fatigue in patients with inflammatory bowel disease is associated with distinct differences in immune parameters

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Background: Although it is well recognized that fatigue is an important problem in many of the quiescent inflammatory bowel disease (IBD) patients, it is unknown whether the immune status is different in fatigued versus non-fatigued patients. In this study, we contrasted various characteristics of the immune system in fatigued against non-fatigued patients with IBD in clinical remission.

Patients and methods: Patients with IBD in clinical remission were phenotyped according to the Montreal classification, and the checklist individual strength-fatigue (CIS-fatigue) was used to assess fatigue (CIS-fatigue ≥ 35). Flow cytometry on peripheral blood samples was used to investigate differences in leukocyte subsets. The expression of various cytokines was determined in stimulated whole blood and serum samples using enzyme-linked immunosorbent assay. Differences between fatigued and non-fatigued patients with IBD were assessed.

Results: In total, 55 patients were included in the fatigue group (FG) and 29 patients in the non-fatigue group (NFG). No differences in demographic and clinical characteristics were observed between the groups. Flow cytometry data showed a significantly lower percentage of monocytes ($p = 0.011$) and a higher percentage of memory T-cells ($p = 0.005$) and neutrophils ($p = 0.033$) in the FG compared with the NFG. Whole blood stimulation showed increased TNF-α ($p = 0.022$) and IFN-γ ($p = 0.047$) in the FG. The median serum level was significantly higher for IL-12 ($p < 0.001$) and IL-10 ($p = 0.005$) and lower for IL-6 ($p = 0.002$) in the FG compared with NFG.

Conclusion: Significant differences in immune profile between fatigued and non-fatigued patients with IBD in clinical remission were found, which point out to a chronically active and Th1-skewed immune system in patients with fatigue. Whether these immune differences are directly involved in the fatigue complaints via immune-to-brain communication pathways remains to be determined. As such, further exploration of the underlying immune effects associated with fatigue is warranted to determine potential treatment options.

Keywords: inflammatory bowel disease, fatigue, leukocyte subsets, cytokines

Introduction

Patients with inflammatory bowel disease (IBD) suffer from an immune-mediated chronic relapsing disease. This disease significantly impairs the health-related quality of life of patients. Fatigue is an important factor negatively affecting the health-related quality of life in these patients.[1–4] With >40% of patients with IBD suffering from fatigue, even when the disease is in remission, further understanding of the etiology of fatigue in IBD is warranted.[1,3,5]

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There is bidirectional communication between the brain and the immune system.

Activation of the immune system could lead to the release of proinflammatory cytokines that act on the brain to induce sickness behavior (including fatigue) or perhaps even lead to depression in vulnerable individuals.[6] In addition, the brain is able to affect the immune system directly by means of neurotransmitters from either the sympathetic or parasympathetic neurons or indirectly via the induction of hormones such as cortisol.[7]

As such, fatigue can affect the immune system and vice versa. If fatigue influences the immune system in IBD, it is well possible that stratification for pharmacological treatment based on fatigue status may improve clinical outcome. If fatigue merely reflects ongoing immune activation in patients with IBD, it might also implicate the potential usefulness of targeted therapy for IBD-related fatigue.

A variety of factors, including disease activity, female sex, psychological well-being, medication use, anemia and sleep difficulties, are known to influence the severity of fatigue in patients with IBD, and interestingly, many of these factors may in turn also affect immune parameters.[3,4,8] Indeed, in other diseases, especially chronic fatigue syndrome (CFS), fatigue and immunity show important correlations.[9–15] The mechanisms by which fatigue status is linked to the immune system remain largely obscure, but in view of the increasing evidence for the existence of a gut–brain axis, it is well possible that in IBD also, fatigue-related effect of the immune system may exist.[16–18] This effect of the immune system was also proposed in fatigued multiple sclerosis and patients with cancer, where higher levels of proinflammatory cytokines were seen in fatigued patients.[19,20]

The observation that in patients with cancer fatigue may persist for years after treatment completion in otherwise healthy individuals is of special interest since it may reflect the remission situation in patients with IBD with regard to disease activity.[21,22] In patients post cancer treatment, elevated levels of markers of inflammation were found in the circulation (IL-1ra, sTNF-RII and IL-6R) and in peripheral blood mononuclear cells (PBMCs) stimulated with lipopolysaccharide (LPS; IL-1b, IL-6 and TNF-α).[23]

Nevertheless, the relation between fatigue status and immune status in IBD remains unexplored, and thus studies on this aspect of IBD are urgently called for. The abovementioned considerations prompted us to investigate whether fatigued patients with IBD differ from non-fatigued patients with IBD with respect to immunity.

Patients and methods

Study design

For this study, we exploited an earlier published study cohort in which the effects of solution-focused therapy on fatigue in patients with IBD were characterized.[24]

The use of this cohort allowed us to include patients with well-characterized fatigue status. Patients from this cohort were asked to participate in this study.

The checklist individual strength (CIS) was used to determine whether a patient suffered from fatigue (CIS-fatigue subscale score ≥ 35).[25]

The CIS is a 20-item patient-reported validated instrument measuring severity of fatigue, motivation, activity level and concentration. The severity of fatigue, measured with the subscale "fatigue", was used as an outcome measure. Patients with a score of ≥ 35 on this subscale were considered to be fatigued. The CIS is a renewed format of the multifactorial fatigue index (MFI), where five questions are differently formulated and all other questions are the same. The CIS is standardized and uses a cut-off score for fatigue in contrast to the MFI.

As described in our earlier published study cohort, fecal calprotectin concentration was measured in the fatigued patients. Levels of <200 mg/g were regarded as compatible with disease remission.[24] The Harvey–Bradshaw index (HBI) < 5 for Crohn's disease or the colitis activity index (CAI) < 10 for ulcerative colitis was used to determine clinical remission of the disease in the non-fatigued patients.[26,27]

Demographics and disease phenotype (Montreal classification) were collected from medical records, and concomitant medication use was investigated using a questionnaire focusing on current medication use and subjective side effects to medication.[28]

After these baseline measurements and measurements on blood samples, the fatigue group (FG) was enrolled in a clinical trial to study the effects of psychotherapy, especially solution-focused therapy on fatigue of which the results have been described.[24] Consecutive patients with IBD from the same hospitals as the fatigue cohort, with a CIS-fatigue score < 35, were enrolled in the non-fatigue group (NFG) for this study. As in the FG, patients of the NFG were aged ≥ 18 years, and the diagnosis of IBD was radiologically or endoscopically/histologically confirmed. Exclusion criteria, as described in the clinical trial, were equal for the FG and NFG.

Differences in baseline measurements between the FG and the NGF included laboratory values. In the NFG patients, only C-reactive protein (CRP) and leukocytes were measured.

This study was conducted in accordance with the protocol International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki and local national regulations governing clinical study conduct and was registered at the medical ethical committee (MEC) of the Erasmus Medical Center (registration number: MEC-2010-107; NL32020.078.10). The protocol was approved by the institutional review board (MEC) of the Erasmus Medical Center. All patients gave written informed consent. Patients were enrolled in the Netherlands from January 2010 to January 2011 by the principal investigator.

Blood collection and stimulation

Following blood drawing, within 24 hours serum was obtained using a coagulation tube and stored at −80°C until further analysis. Serum was collected from both fatigued and non-fatigued patients with IBD, and immune assays were conducted at the same location for all blood samples.

Heparinized whole blood samples were diluted 1:10 with Roswell Park Memorial Institute (RPMI) 1640 (Lonza, Basel, Switzerland) and were stimulated with 25 µg/mL phytohemagglutinin (PHA; Remel, Lenexa, KS, USA) or 100 ng/ mL LPS (Sigma-Aldrich, Zwijndrecht, the Netherlands). Supernatants of the LPS- and PHA-stimulated cultures were obtained at 24 and 72 hours, respectively, and stored at −80°C until further analysis.

Leukocyte subsets analysis

After removal of erythrocytes using ery-lysis buffer, the heparinized whole blood samples were stained using antibodies against CD16 (Pacific Blue), CD14 (PerCP/Cy5.5), CD56 (PE/Cy7) and CD62-L (Alexa Fluor 647) purchased from BioLegend (San Diego, CA, USA); CD3 (AmCyan) and CD4 (APC-H7) purchased from BD Biosciences (Franklin Lakes, NJ, USA); CD45RA (FITC) purchased from eBioscience (San Diego, CA, USA) and CD19 (PE) purchased from Beckman Coulter (Brea, CA, USA) to analyze the different leukocyte subsets using the FACSCanto II flow cytometer with FACSDiva software from BD Biosciences. The different leukocyte subsets were identified and counted using FlowJo software (Tree Star, Inc., Ashland, OR, USA).

The leukocytes were subdivided into three main populations based on forward scatter and side scatter: lymphocytes, granulocytes and monocytes. The different leukocyte subsets were subdivided into lymphocytes (T-cells, B-cells, cytotoxic T-cells, T-helper cells, memory T-cells, effector T-cells, naïve T-cells and NK-cells), monocytes (CD14+CD16+, CD14−CD16+ and CD14+CD16−) and granulocytes (eosinophils and neutrophils) as shown in Table 1.

Cytokine levels

Serum and supernatant levels of IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α and IFN-γ were assessed using Ready-Set-Go!® enzyme-linked immunosorbent assay sets from eBioscience according to the manufacturer's instructions and using MaxiSorp 96-well plates (Nunc; Thermo Fisher Scientific, Waltham, MA, USA) and a model 680 microplate reader from Bio-Rad (Hercules, CA, USA). When levels were below the detection limit of 2.0, these were considered left-hand censored.

Statistical analysis

For differences in characteristics and disease phenotypes between the FG and NFG, χ^2 tests were used for dichotomous variables and *t*-tests for continuous variables.

Normality of laboratory parameters, leukocyte subsets and cytokines were determined using Shapiro–Wilk tests. All outcomes, except lymphocytes, granulocytes, monocytes, naïve T-cells and memory T-cells, were not normally distributed. Differences between the FG and NFG were analyzed with *t*-tests for normally distributed outcomes and with Mann–Whitney *U* tests for abnormally distributed outcomes. A number of laboratory parameters for serum cytokines were below the detectable range of 2.0. For these parameters, we performed Tobit analyses for low-censored data on the rank-transformed variables.[29] Median values, interquartile ranges and differences are presented in Table 1.

Tobit analyses were performed with Stata version 13.1 (SataCorp LP, College Station, TX, USA). All other analyses were performed with SPSS software for Windows, V.20 (SPSS, Chicago, IL, USA).

Results were considered significant when two-sided *p*-values were <0.05; no correction for multiple testing was applied because of the exploratory nature of the study.

Results

Patient characteristics

In total, 55 fatigued patients with IBD (FG) of the earlier published study cohort agreed to participate in this study, and 29 patients in the NFG were included.

Before analyzing the differences in immune parameters, the demographic and clinical characteristics of the groups were analyzed (FG vs. NFG; Tables 2 and 3). No differences were observed between the two groups. With regard to remission of the disease, the NFG showed a mean CAI score of 2.3 (standard deviation [sd] 0.6) and an HBI score of 1.2 (sd 1.1).

Table 1 Leukocyte subsets and cytokines

Baseline	Fatigue (n = 55)		Non-fatigue (n = 29)		*p*-value
	Median	[Interquartile range]	Median	[Interquartile range]	
Lymphocytes	33.2	[22.8–46.0]	35.0	[28.7–50.7]	0.188
NK-cells	2.7	[0.4–6.6]	4.7	[0.9–8.2]	0.171
B-cells	8.5	[4.7–11.2]	8.6	[4.4–12.4]	0.158
T-cells	78.3	[59.5–82.4]	77.8	[66.2–82.7]	0.963
Leukocytes	6.0	[5.1–7.6]	5.4	[4.5–7.2]	0.862
T-helper cells	64.4	[57.4–71.3]	67.6	[54.3–74.8]	0.519
Naïve T-cells	36.1	[26.5–43.0]	47.0	[29.2–58.1]	0.062
Memory T-cells*	43.7	[36.4–49.9]	33.7	[27.9–39.6]	0.005
Effector T-cells	16.5	[10.3–23.6]	12.8	[8.2–23.0]	0.263
Cytotoxic T-cells	35.6	[28.7–42.6]	32.4	[25.2–45.7]	0.527
Granulocytes	46.6	[34.2–58.6]	40.5	[28.5–52.6]	0.351
Eosinophils	3.6	[2.5–6.7]	4.9	[2.7–11.8]	0.097
Neutrophils*	77.0	[64.6–83.6]	68.8	[58.9–78.2]	0.033
Monocytes*	5.3	[3.5–7.5]	7.2	[4.7–9.1]	0.011
CD14– CD16+*	7.9	[5.7–11.5]	11.9	[7.9–15.3]	0.017
CD14+ CD16+*	3.5	[2.8–6.6]	2.6	[2.1–4.0]	0.010
CD14+ CD16–	86.9	[82.2–91.3]	84.6	[80.8–90.5]	0.361
PHA-stimulated WB					
IL-5	118.1	[86.5–211.2]	85.6	[62.3–148.7]	0.078
IL-6	2452	[1629–13758]	3464	[1224–15218]	0.982
IL-8	57143	[41054–94130]	46237	[23679–85122]	0.156
IL-10	658	[326–1108]	276	[154–1133]	0.132
TNF-α*	224	[112–678]	125	[48–438]	0.022
IFN-g*	28875	[17487–51398]	9536	[2525–75476]	0.047
LPS-stimulated WB					
IL-6	3115	[2394–5276]	5065	[3287–7268]	0.046
IL-8	5844	[2816–9539]	4760	[3067–10641]	0.777
IL-10	200	[107–304]	136	[96–275]	0.651
TNF-α	560	[174–1208]	206	[66–709]	0.073
Serum cytokines (% below detectable range in FG and NFG)					
IL-4 (64%–71%)	2.0	[2.0–3.2]	2.0	[2.0–2.4]	0.570
IL-5 (19%–25%)	14.7	[3.2–54.0]	10.0	[2.0–27.6]	0.269
IL-6* (83%–42%)	2.0	[2.0–2.0]	2.3	[2.0–4.7]	0.002
IL-8 (28%–29%)	2.6	[2.0–4.8]	5.7	[2.0–50.7]	0.122
IL-10* (42%–67%)	2.2	[2.0–3.1]	2.0	[2.0–2.4]	0.005
IL-12* (4%–33%)	4.8	[3.8–9.0]	3.3	[2.0–4.4]	<0.001
TNF-α (49%–4%)	49.5	[11.9–94.1]	45.1	[13.5–174.2]	0.498
IFN-g (15%–29%)	4.6	[2.8–7.3]	3.3	[2.0–10.8]	0.293

Notes: Unpaired two samples *t*-test for normally distributed variables (lymphocytes, granulocytes, monocytes, naïve T-cells and memory T-cells). Mann–Whitney *U* test for not normally distributed variables. Tobit test for serum cytokines with low-censored values. *$p < 0.05$. Lymphocytes, granulocytes and monocytes: percentage of whole blood. CD14+ CD16+ and CD14+ CD16- monocytes: percentage of total monocytes. T-helper cells and cytotoxic T-cells: percentage of T-cells. Naïve T-cells, memory T-cells and effector T-cells: percentage of T-helper cells. Eosinophils and neutrophils: percentage of granulocytes. CD14- CD16+, CD14+ CD16+ and CD14+ CD16- monocytes: percentage of total monocytes. Cytokine concentrations are in pg/mL.

Abbreviations: n, number of patients; PHA, phytohemagglutinin; WB, whole blood; LPS, lipopolysaccharide; FG, fatigue group; NFG, non-fatigue group.

The mean calprotectin level in the FG was 66 µg/g. Based on these scores, both groups were in clinical remission.

Whole blood leukocytes

As a first crude indicator of a link between fatigue status and the immune system in patients with IBD, the composition of the leukocyte system was investigated using flow cytometry. No differences were detected in total leukocyte numbers (Table 1) between the groups. Within the major leukocyte subpopulations (lymphocytes, granulocytes and monocytes), a significant lower percentage of monocytes (median: FG: 5.3, NFG: 7.2; $p = 0.011$) was detected in the FG compared with the NFG. When monocytes were further subphenotyped, we found a significant lower percentage of the non-classical $CD14^{dim}$ $CD16^{+}$ monocytes in the FG compared with the NFG (median: FG: 7.9, NFG: 11.9; $p = 0.017$).

Within the lymphocyte subsets, no differences were detected; only within the CD4+ (helper) T-cell population,

Table 2 Patient characteristics

Patient characteristics	Fatigue (n = 55)	Non-fatigue (n = 29)	*p*-value
Age in years; mean (sd)	40.1 (10.4)	40.7 (14.4)	0.861
Females, n (%)	36 (65%)	13 (45%)	0.068
Crohn's disease, n (%)	42 (76%)	26 (90%)	0.140
Ulcerative Colitis, n (%)	13 (24%)	3 (10%)	
Current medication use, n (%)			
5-ASA	20 (36%)	10 (34%)	0.954
Immunosuppressives	20 (36%)	13 (45%)	0.376
Corticosteroids	10 (18%)	5 (17%)	0.971
Biologicals (anti-TNF)	13 (24%)	9 (31%)	0.406
Side effects to medication, n (%)			
5-ASA	3 (5%)	1 (3%)	0.484
Immunosuppressives	11 (20%)	7 (24%)	0.402
Corticosteroids	3 (5%)	3 (10%)	0.876
Biologicals (anti-TNF)	8 (15%)	3 (10%)	0.066
Disease activity, n			
CAI	14, 4 (mean)	4, 2.3 (mean)	0.805
HBI	41, 2.8 (mean)	25, 1.2 (mean)	0.035

Notes: Chi-square test for dichotomous variables and *t*-test for continuous variables. Corticosteroids: prednisone and budesonide. Immunosuppressives: azathioprine, methotrexate and cyclosporine.
Abbreviations: n, number of patients; sd, standard deviation; 5-ASA, 5-aminosalicylic acid; CAI, colitis activity index; HBI, Harvey–Bradshaw index.

Table 3 Disease phenotype

Montreal classification	Fatigue (n = 55)	Non-fatigue (n = 29)	*p*-value
Montreal classification – CD[28]			
Mean age at diagnosis in yrs (sd)	27.4 (9.2)	24.0 (9.0)	0.135
Age at diagnosis, n (%)			
A1	4 (9.8)	7 (26.9)	0.065
A2	31 (75.6)	18 (69.2)	0.566
A3	6 (14.6)	1 (3.8)	0.159
Location			
L1	4 (9.8)	3 (11.5)	0.816
L2	17 (41.5)	9 (34.6)	0.575
L3	20 (48.8)	13 (50.0)	0.922
L4	1 (2.4)	1 (3.8)	0.742
+L4	40 (2.4)	23 (11.5)	0.126
Behavior			
B1	28 (68.3)	15 (57.7)	0.378
B2	6 (14.6)	6 (23.1)	0.380
B3	6 (14.6)	5 (19.2)	0.621
p	30 (26.8)	17 (34.6)	0.497
Surgery CD			
Bowel resection (%)	46.3	61.5	0.225
Number of resections; mean (sd)	1 (0.9)	1.5 (1.1)	0.122
Age at first resection; mean (sd)	29.8 (9.7)	29.5 (13.1)	0.930
Stoma (%)	14.6	15.4	0.933
Rectum amputation (%)	7.3	7.7	0.955
Montreal classification – UC[28]			
Mean age at diagnosis in yrs (sd)	29.2 (8.1)	35.7 (6.0)	0.215
Age at diagnosis, n (%)			
A1	0 (0)	0 (0)	
A2	13 (92.3)	2 (66.7)	0.226
A3	1 (7.7)	1 (33.3)	0.226
Location			
E1	1 (7.7)	0 (0)	0.620
E2	8 (53.8)	3 (100)	0.137
E3	5 (38.5)	0 (0)	0.195
Severity			
S0	7 (46.2)	0 (0)	0.137
S1	7 (53.8)	2 (66.7)	0.687
S2	0 (0)	1 (33.3)	0.032
S3	0 (0)	0 (0)	
Surgery UC			
Bowel resection (%)	7.1	0	0.633
Number of resections, mean	1	0	–
Age at first resection, mean	22	–	–
Stoma (%)	0	0	–
Rectum amputation (%)	0	0	–
Laboratory CD and UC			
CRP; median [interquartile range] – baseline	1.0 [0.0–2.0]	2.0 [1.0–3.0]	0.140
Leukocytes; median [interquartile range] – baseline	6.0 [5.1–7.6]	5.4 [4.5–7.2]	0.188

Notes: Chi-square test for dichotomous variables. Mann–Whitney *U*-test for the continuous variables, CRP and leukocytes. *t*-test for all other continuous variables.
Abbreviations: n, number of patients; CD, Crohn's disease; yrs, years; sd, standard deviation; UC, ulcerative colitis; CRP, C-reactive protein.

a significantly higher percentage of central memory CD4+ T cells (median: FG: 43.7, NFG: 33.7; $p = 0.005$) in the FG compared with the NFG was found. Further analysis of the granulocyte population showed a significantly higher percentage of neutrophils (median: FG: 77.0, NFG: 68.8; $p = 0.033$) in the FG compared with the NFG.

Whole blood cytokine production

In addition to the leukocyte subset analysis, we also determined the production of cytokines by the leukocytes after stimulation with PHA or LPS, in which PHA stimulates mostly lymphocytes and LPS is more prone to trigger the innate granulocytes and monocytes to produce cytokines (Table 1). PHA stimulation induced higher median cytokine levels in whole blood from the FG for all cytokines measured except for IL-6. Of these cytokines, the levels of TNF-α (median: FG: 224, NFG: 125; $p = 0.022$) and IFN-γ (median: FG: 28875, NFG: 9536; $p = 0.047$) were significantly higher in the FG compared with the NFG. LPS stimulation induced significantly higher median IL-6 levels in the NFG compared with the FG (median: FG: 3114, NFG: 5064; $p = 0.046$)

Serum cytokine levels

We also investigated the serum levels of a variety of cytokines (Table 1). The levels of IL-12 (median: FG: 4.8, NFG: 3.3; $p < 0.001$) and IL-10 (median: FG: 2.2, NFG: 2.0 [lower limit]; $p = 0.005$) were significantly higher in the FG serum samples, whereas the levels of IL-6 were significantly reduced in the FG serum compared with the NFG serum (median: FG: 2.0 [lower detection limit], NFG: 2.3; $p = 0.002$).

Discussion

A large portion of patients with IBD suffer from fatigue even when the disease is in clinical remission. The intricate bidirectional relation between the immune system and the brain justifies the search for possible difference in immune parameters in these patients.

Activation of the immune system could lead to the release of proinflammatory cytokines that act on the brain to induce sickness behavior (including fatigue) or maybe even lead to depression in vulnerable individuals.[6] In addition, the brain is able to affect the immune system directly by means of neurotransmitters from either the sympathetic or parasympathetic neurons or indirectly via the induction of hormones such as cortisol.[7]

We compared a large variety of immune parameters between fatigued and non-fatigued patients with IBD to determine whether there were parameters that were discriminative between the groups.

Since we are the first to compare a large variety of immune parameters between patients with IBD with fatigue and without fatigue, we can only mirror our data to those studies that assessed immune parameters in patients suffering from fatigue in different disease settings such as cancer, CFS and chronic viral infections.[9–15,30–36]

Since viral infections are a popular proposed cause of CFS, it was interesting to notice that naïve CD4 cells and enhanced memory cells are a sign of chronic adaptive immune activation and have been previously reported in patients with chronic hepatitis C infection and were associated with cytomegalovirus and *Helicobacter pylori titers*.[37–39] As such, these data support the idea that there may still be some ongoing immune activation of unknown origin involved in the fatigue complaints. Indeed, fatigued cancer survivors showed a 31% increase in circulating T lymphocytes relative to non-fatigued controls, particularly CD4+ T lymphocytes (41% increase) and CD56+ effector T lymphocytes (52% increase).

As with the T-cell changes, differences in neutrophils and monocytes between fatigued and non-fatigued patients could all be pointing toward an ongoing infection in the fatigued patients with IBD.

Both the significantly enhanced TNF-α and IFN-γ release upon stimulation with PHA are in line with observations in CFS patients where PBMCs instead of whole blood were stimulated.[40] Both of them are also supportive of a Th1-skewed immunity driving the fatigue complaints in patients with IBD.

With regard to the serum proinflammatory cytokine levels, no significant difference in the levels of TNF-α was observed as often reported in CFS.[41,42] However, anti-TNF treatment could influence these results.

The enhanced IL-12 serum levels in fatigued patients with IBD were also in line with data previously reported on plasma of CFS patients compared to healthy controls.[10] Although the reduced IL-6 levels were in contrast with this study, reduced IL-6 levels were reported in a recent study when moderate CFS patients were compared with healthy controls.[10,43]

The differences in immune parameters between the fatigued and non-fatigued patients with IBD suggest that there is a link between the immune system and the brain in IBD-associated fatigue. Whether this is a direct link cannot be concluded from our data.

Most of our data support the hypothesis that there is an ongoing low level of immune activation in patients with IBD who present fatigue complaints while in clinical remission. Because of the multifactorial origins of fatigue, there could be a variety of causes of the observed immune activation that may even differ between patients presenting similar immune parameters. Viral infections either acute or chronic may be involved in the IBD-associated fatigue.[38,44] Since serology status for different viral infections was not obtained during this study, we cannot rule out their possible role in at least subsets of the fatigued patients. Another possible cause may be the occurrence of microscopic relapses, at the level of the lamina propria, without affecting clinical disease symptoms.[45] Since our patients were in clinical remission, no biopsies are available to rule out this possibility. Microscopic disease activity may enable enhanced translocation of bacteria, described as "leaky gut", a phenomenon that has been associated with CFS as well.[46,47]

Since microbes are well known to influence the immune system, it will be interesting to include characterization of the microbiome in future studies focusing on fatigue in IBD or even consider testing therapeutic microbes for treatment of IBD-related fatigue.[41,48]

Conclusion

We show for the first time that differences in immune parameters are associated with fatigue symptoms in patients with IBD without clinically active disease. These data warrant further investigation into the possible causal relations between these parameters and the fatigue symptoms since this may lead to an effective resolution in part of the patients with IBD with fatigue.

Disclosure

The authors report no conflicts of interest in this work.

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