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ORIGINAL ARTICLE

Case Control Study

Cerebral magnetic resonance imaging in quiescent Crohn's disease patients with fatigue

Sanne van Erp, Ece Ercan, Perla Breedveld, Lianne Brakenhoff, Eidrees Ghariq, Sophie Schmid, Matthias van Osch, Mark van Buchem, Bart Emmer, Jeroen van der Grond, Ron Wolterbeek, Daniel Hommes, Herma Fidder, Nic van der Wee, Tom Huizinga, Désirée van der Heijde, Huub Middelkoop, Itamar Ronen, Andrea van der Meulen-de Jong

Sanne van Erp, Lianne Brakenhoff, Daniel Hommes, Andrea van der Meulen-de Jong, Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, Zuid-Holland 2333 ZA, the Netherlands

Ece Ercan, Perla Breedveld, Eidrees Ghariq, Sophie Schmid, Matthias van Osch, Itamar Ronen, C.J. Gorter Center, Leiden University Medical Center, Leiden, Zuid-Holland 2333 ZA, the Netherlands

Ece Ercan, Perla Breedveld, Eidrees Ghariq, Sophie Schmid, Matthias van Osch, Mark van Buchem, Bart Emmer, Jeroen van der Grond, Itamar Ronen, Department of Radiology, Leiden University Medical Center, Leiden, Zuid-Holland 2333 ZA, the Netherlands

Ron Wolterbeek, Department of Medical Statistics, Leiden University Medical Center, Leiden, Zuid-Holland 2333 ZA, the Netherlands

Daniel Hommes, Center for Inflammatory Bowel Diseases, University of California Los Angeles, Los Angeles, CA 90095, United States

Herma Fidder, Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht 3584 CX, the Netherlands

Nic van der Wee, Department of Psychiatry, Leiden University Medical Center, Leiden, Zuid-Holland 2333 ZA, the Netherlands

Tom Huizinga, Désirée van der Heijde, Department of Rheumatology, Leiden University Medical Center, Leiden, Zuid-Holland 2333 ZA, the Netherlands

Huub Middelkoop, Department of Neuropsychology, Leiden University Medical Center, Leiden, Zuid-Holland 2333 ZA, the Netherlands

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Correspondence to: Dr. Sanne van Erp, Department of Gastroenterology and Hepatology, Leiden University Medical Center, Albinusdreef 2, Leiden 2333 ZA, the Netherlands. s.j.h.van_erp@lumc.nl

Telephone: +31-71-5262915
Fax: +31-71-5248115

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Abstract

AIM

To evaluate brain involvement in quiescent Crohn's disease (CD) patients with fatigue using quantitative magnetic resonance imaging (MRI).

METHODS

Multiple MRI techniques were used to assess cerebral changes in 20 quiescent CD patients with fatigue (defined with at least 6 points out of an 11-point numeric rating scale compared with 17 healthy age and gender matched controls without fatigue. Furthermore, mental status was assessed by cognitive functioning, based on the neuropsychological inventory including the different domains global cognitive functioning, memory and executive functioning and in addition mood and quality of life scores. Cognitive functioning and mood status were correlated with MRI findings in the both study groups.

RESULTS

Reduced glutamate + glutamine (Glx = Glu + Gln) concentrations (P = 0.02) and ratios to total creatine (P = 0.02) were found in CD patients compared with controls. Significant increased Cerebral Blood Flow (P = 0.05) was found in CD patients (53.08 ± 6.14 mL/100 g/min) compared with controls (47.60 ± 8.62 mL/100 g/min). CD patients encountered significantly more depressive symptoms (P < 0.001). Cognitive functioning scores related to memory (P = 0.007) and executive functioning (P = 0.02) were lower in CD patients and both scores showed correlation with depression and anxiety. No correlation was found subcortical volumes between CD patients and controls in the T_1-weighted analysis. In addition, no correlation was found between mental status and MRI findings.

CONCLUSION

This work shows evidence for perfusion, neurochemical and mental differences in the brain of CD patients with fatigue compared with healthy controls.

Key words: Magnetic resonance imaging; Systemic inflammation; Fatigue; Crohn's disease; Cognition

Core tip: The present study explores perfusion, neurochemical and mental differences in the brain of Crohn's disease (CD) patients compared with healthy controls. This implies that for a gastroenterologist it is important to focus, besides gastrointestinal symptoms due to inflammation, on the effects of systemic inflammation on the brain and mental status. Knowledge and understanding of these effects in CD patients may help health professionals to set up interventions to maintain CD remission and improve mental status by *e.g.* psychosocial interventions.

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INTRODUCTION

Crohn's disease (CD) is a relapsing inflammatory bowel disease (IBD)[1], characterized by segmental transmural lesions that can affect any part of the gastrointestinal tract[2]. Besides gastrointestinal symptoms, fatigue is common in CD patients. In contrast to regular fatigue which affects nearly everyone, disease-related fatigue is more long lasting and may occur despite sufficient sleep and rest. Generally, fatigue lasting for more than 6 mo is considered chronic and is significantly more prevalent in IBD patients than in healthy controls[3]. Although fatigue is influenced by IBD disease activity, 40% of the patients with quiescent disease report fatigue as well and contributes negatively to the patients' health-related quality of life (QoL)[4,5].

The pathogenesis of CD is multifactorial and results from an impaired interaction between environment, commensal microbiota and the human immune system, leading to a chronic inflammatory status and eventually CD[6,7]. Furthermore, in both quiescent and active CD patients increased levels of circulating inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) are reported[8-10]. Although quiescent CD patients report fewer clinical symptoms and score less on the clinical activity score compared with active CD patients, inflammatory cytokines are present[9,10]. TNF-α can be secreted by a large variety of cells[8] and can initiate a signalling stimulus to the brain parenchyma that will subsequently activate microglia. Activated microglia stimulates the production of monocyte chemo-attractant protein (MCP)-/CCP2, which recruits monocytes into the brain[9-11]. Moreover, this cerebral infiltration of monocytes plays an important role in driving inflammation in the brain[11-13].

Magnetic resonance imaging (MRI) is an imaging technique widely used to visualize the effect of several neurological diseases, such as Multiple Sclerosis (MS), Parkinson's Disease and Alzheimer disease, in the brain[14]. A variety of MRI methods can be employed to identify cerebral changes due to a specific disease. These methods include T_1-weighted imaging, magnetization transfer imaging (MTI), magnetic resonance spectroscopy (MRS), arterial spin labeling (ASL) and diffusion tensor imaging (DTI). T_1-weighted imaging provides high-resolution, high-contrast anatomical images of the brain and can be used to determine the volumes of the grey matter (GM), white matter (WM), cerebral spinal fluid (CSF) and subcortical structures[15]. Through voxel based morphometry (VBM), it is possible to visualize local changes in GM volumes[16]. MTI is a technique sensitive to brain tissue microstructural changes, stemming from changes in macromolecules such as myelin or cell membranes[17]. MRS measures the concentration of certain metabolites in living tissues and gives evidence for neurochemical changes[18]. ASL is a non-invasive tool for the quantification of regional cerebral blood flow (CBF)[19] and can reveal changes in tissue perfusion. DTI is sensitive to minute changes in tissue microstructure, such as changes in myelin integrity and axonal density in white matter fiber tracts, based on the random motion or diffusion of water molecules[20].

Previous MRI studies have shown that systemic inflammation contributes to cognitive decline, for example in relation to aging[21], but also to brain diseases including Alzheimer disease, MS and Parkinson's disease by promoting activation of the immune system[22-24]. Metabolic and cerebral perfusion changes have been found in the brain of patients with Rheumatoid Arthritis (RA), Systemic Sclerosis and Systemic Lupus Erythematosus (SLE)[11,12,25-31]. In addition, previous studies performed in patients with Chronic Fatigue Syndrome (CFS) found an association between fatigue complaints and metabolic changes in the brain as well[32-34]. In CFS patients, the mean ratio of choline (Cho) to creatine (Cr) in the occipital cortex was significantly higher than in controls, indicating an abnormality of phospholipid metabolism in the brain in CFS[32-33]. These findings suggest that systemic inflammation and fatigue complaints could have structural, neurochemical and functional correlates in the brain. So far, the link between systemic inflammation, disease-induced fatigue and changes in the brain have not been explored in CD patients. The aim of this exploratory study was to investigate to what extent systemic inflammation affects the brain of quiescent CD patients, by using a variety of MRI acquisition methods and neuropsychological examinations that assess cognition, mood and QoL. Furthermore, the correlation between MRI changes, clinical characteristics, including fatigue scores, and mental status was investigated.

MATERIALS AND METHODS

Study population and study design

In this case-control study 20 CD patients and 17 age and gender matched healthy controls were included. Since it is known from literature that there is an age associated decrease in brain volume, primarily caused by a decrease in neuronal size and partly due to a reduction in numbers of neurons caused by apoptosis[35], a correction was made for this confounder by matching the subjects.

Consecutive CD patients, fulfilling the inclusion criteria, were recruited through the IBD outpatient clinic of the department of Gastroenterology and Hepatology of the Leiden University Medical Center (LUMC), the Netherlands. The patients had endoscopic proven CD for at least 3 mo before inclusion, were in clinical remission and experienced fatigue. CD patients with anemia (Hb < 7.0 mmol/L), primary sclerosing cholangitis and routine MRI-contraindications (*e.g.,* instable metal implants or a pacemaker) were excluded. All medication deemed necessary by the gastroenterologist was allowed at study inclusion, except for anti-TNFα or corticosteroid use, since this medication could reduce systemic inflammation the most and thus influence clinical disease activity. Healthy controls were recruited *via* an advertisement in het LUMC and included in the study if they had no anamnestic brain abnormalities, nervous system disease or chronic inflammation in the body. A 1-d program was set up for all participants by the relevant medical specialists, including a gastroenterologist, radiologist, psychiatrist and neuropsychologist and all individuals were asked to complete several questionnaires at study inclusion about demographics, mental status and QoL. This study was approved by the institutional medical ethical committee of the LUMC and all patients signed a written informed consent prior to study enrolment.

Clinical characteristics

Disease activity: The clinical disease activity of the CD patients was measured with the Harvey-Bradshaw Index (HBI). The HBI consists of 12 criteria, which include general well-being, abdominal pain, daily number of liquid stools, abdominal mass and extra intestinal manifestations (arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula and abscess). Patients with an HBI score of 4 or less were classified as having quiescent CD disease[36].

Fatigue: Fatigue was assessed with the Multidimensional Fatigue Index (MFI) and the Visual Analogue Scale (VAS). The MFI is a self-report measurement containing 20 questions consisting of 5 subscales covering different dimensions: general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. The questions are about the fatigue experienced by the subject in the 7 d prior to examination.

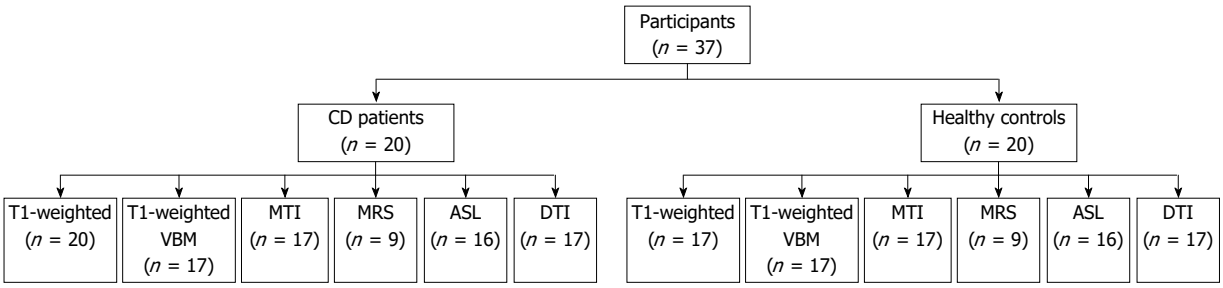

Figure 1 Flowchart of included participants in the magnetic resonance imaging analyses. CD: Crohn's disease; VBM: Voxel based morphometry; MTI: Magnetization transfer images; MRS: Magnetic resonance spectroscopy; ASL: Arterial spin labelling; DTI: Diffusion tensor imaging.

Scores range from 4 to 20, with higher scores indicating higher levels of fatigue[37]. The VAS consists of a 10 point self-rating scale that measures subjective experiences of fatigue. The participants had to indicate on a visual line how they were currently feeling. Six points or more indicated the presence and experience of fatigue in individuals[38].

MRI data acquisition

All study subjects underwent MRI of the brain, using a Philips Ingenia 3.0 Tesla MRI Scanner (Philips Medical Systems, Best, The Netherlands) equipped with a 12 channel head coil, and images were evaluated by an experienced neuroradiologist (MvB). The MRI protocol consisted of T_1-weighted imaging, MTI, MRS, ASL and DTI, and lasted for about 60 min. Since more CD patients were included and all patients and healthy controls were age-gender matched, in total 3 CD patients, who matched the least with the controls, got excluded from the voxel-based analysis of the T_1-weighted and DTI data. For the MRS and ASL analyses data of some CD subjects were either missing because of time limitations or excluded due to low quality, caused by subject motion. For the MRS analysis only 9 CD patients and 9 age and gender matched controls were included, and for the ASL analysis 16 CD patients and 16 age and gender matched controls were included (Figure 1). The MRI scan protocol consisted of (1) axial 3D T1-weighted images (FOV: 224 mm × 144 mm × 182 mm, resolution: 0.88 mm × 0.88 mm × 1.20 mm, TR/TE = 9.75/4.59 ms); (2) sagittal FLAIR images (FOV: 224 mm × 144 mm × 180 mm, resolution: 0.5 mm × 0.5 mm × 3.6 mm, TR/TE/TI = 10000/120/1650 ms); (3) axial DTI (FOV: 176 mm × 144 mm × 224 mm, resolution: 1.75 mm × 1.75 mm × 3.6 mm, TR/TE = 4317/55.33 ms, one volume with b = 0 s/mm^2 and 32 diffusion-weighted volumes with b = 800 s/mm^2); (4) axial MTI (FOV: 224 × 144 × 180, resolution: 0.88 mm × 0.88 mm × 7.2 mm, TR/TE = 100/10.95 ms, two volumes acquired one with and one without a radiofrequency saturation pulse); (5) ASL (FOV: 240 mm × 240 mm × 133 mm, resolution: 3.0 mm × 3.0 mm × 7.0 mm, TR/TE = 4000/15.19 ms, labeling duration = 1650 ms, post-labeling delay = 1525 ms, 35 label and control pairs and background suppression inversion pulses at 50 and 1150 ms); and (6) a single volume, stimulated echo acquisition mode (STEAM) ^{1}H MRS scan with a volume of interest (VOI) located in the left centrum semi ovale, containing mostly white matter as shown in Figure 2 (voxel size = 30 mm × 15 mm × 15 mm, TR/TE = 2000/14 ms, mixing time = 19 ms, sample size = 2048, number of averages = 96).

Post-processing and data analysis

T_1-weighted image analysis: Brain extraction tool (BET) of FMRIB Software Library (FSL) (http://www.fmrib.ox.ac.uk/fsl) was used to extract the brain tissue from T_1-weighted images[15]. FSL FMRIB's Automated Segmentation Tool (FAST)[39] was used to segment GM, WM and CSF tissues from the brain extracted T_1-weighted images. FSL FMRIB's Integrated Registration and Segmentation Tool was used to segment subcortical structures: nucleus accumbens, amygdala, caudate, hippocampus, globus pallidus, putamen and thalamus[40]. Following segmentation, the volumes of GM, WM and subcortical structures were calculated using FSL Maths. The volumes were normalized to subject intracranial volume by dividing the volumes with the total brain volume of the same subject. VBM in FSL was used to assess local GM differences between CD patients and controls[16,41].

MTI analysis: MTI were split into images with and without saturation. Both images, with and without saturation, were brain extracted with BET and the image without saturation was aligned to the image with saturation. After alignment, the magnetization transfer ratio (MTR) of the whole brain was calculated using FSL Maths. The MTR images were then registered to the T_1-weighted images from the same subject with FLIRT[42]. Subsequently, MTR images were multiplied with the binary GM and WM masks from the same subject, to create GM and WM MTR images. Tissue-specific histograms of MTR values from the GM and WM of patients and controls were created using an in house-developed MATLAB® program (Mathworks, Natick, MA, United States).

MRS analysis: The MRS analysis was performed

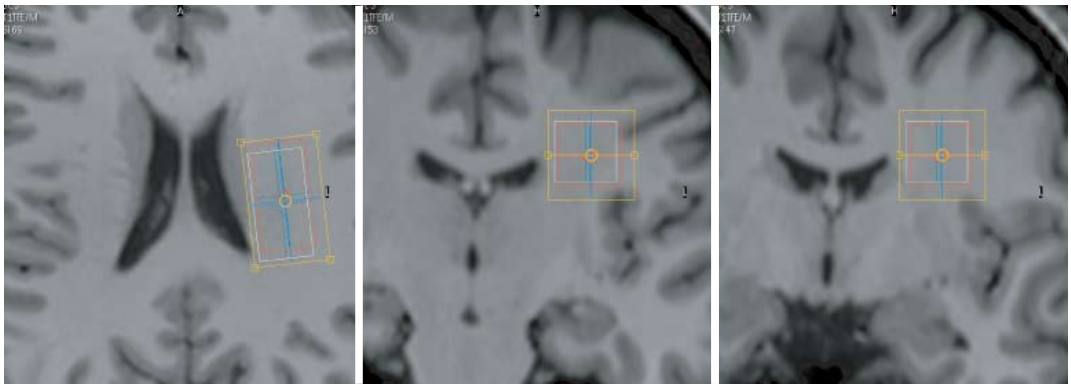

Figure 2 Planning of the ^{1}H-magnetic resonance spectroscopy volume of interest in the left centrum semi-ovale. Seen on axial (left) and on the coronal (right) T_1-weighted image slices. The effective volume of interest set at the tNAA frequency is shown (red rectangle) together with the shimming volume (yellow rectangle).

in MATLAB and LCmodel[43]. An in-house developed MATLAB code was used to calculate and correct for GM, WM and CSF tissue fraction (%) within the VOI for each subject separately. LCmodel was used for the calculation of the concentration and ratio to total creatine (tCr) of the metabolites N-acetyl-aspartate (NAA), creatine (Cr), glutamate (Glu), myo-inositol (Ins), glutamine (Gln), N-acetyl-aspartyl-glutamate (NAAG) and choline (Cho). Institutional units (IU) of concentration were expressed in mmol. Among these metabolites, NAA is a neuronal marker, NAAG is suggested to be related to excitatory neurotransmission, total Creatine (tCr), the sum of phosphocreatine and creatine, is a marker of energy metabolism. Cho is related to cell membrane turnover, Glu is an excitatory neurotransmitter predominantly found in neurons, Gln is a precursor for Glu and found mostly in astrocytes, and Ins is a possible astrocytic marker[44]. The mean ratios of NAA, Glu, Ins, Gln, NAAG and Cho to tCr were compared between the two study groups.

ASL analysis: The average GM Cerebral Blood Flow value was calculated in FSL[45]. The ASL label and control images were motion corrected by FSL MCFLIRT[46]. The perfusion maps were calculated for each subject by subtracting the label from the control images and averaging those images. Following that, perfusion maps from each subject were registered first linearly and then nonlinearly to GM volume segmented from the T_1-weighted image of the subject and subsequently they were first linearly and then nonlinearly registered to average brain template from the Montreal Neurological Institute (MNI). CBF of the GM is calculated by using a binary GM mask of the subject with a threshold of 60% GM probability and using the following equation:

$$CBF_{pCASL} = \frac{6000 \cdot \lambda \cdot \Delta M \cdot e^{(PLD/T_{1a})}}{SI_{PD} \cdot 2 \cdot \alpha_{pCASL} \cdot T_{1a} \cdot \alpha_{BSup} \cdot (1 - e^{-(\tau/T_{1a})})}$$

Where λ is the blood/brain partition coefficient in mL/g which was 0.9, ΔM is the signal intensity of the control image subtracted with the signal intensity of the label image, the post labelling delay was 1525 ms. T_1a is the longitudinal relaxation time of the blood was 1664 ms, SI_{PD} is the signal intensity of a proton density-weighted image and τ is the label duration which was 1650 ms. A_{pCASL} is the labelling efficiency, which was 0.85 and α_{BSup} was 0.83. A comparison of GM CBF was made between the patients and controls.

Diffusion tension images analysis: ExploreDTI software[47] was used for motion and distortion correction of the DTI images and for calculating the Fractional Anisotropy (FA) and Mean Diffusivity (MD) maps. FA and MD maps were used as an input to tract-based spatial statistics processing[48], which was carried out in FSL. The FA maps were first linearly registered with an affine transformation, subsequently non-linearly registered to the MNI space, and a mean FA skeleton was created. For each subject, the FA map was projected on the skeleton. Following that, randomisation was used to perform *t*-test based voxel-wise comparison of the FA skeletons between patients and controls. The same procedure was repeated for MD maps.

Assessment of cognitive performance

Cognition: Several neuropsychological assessments were conducted in both healthy controls and CD patients and evaluated by an experienced clinical neuropsychologist (HM). The examination took approximately one hour and included validated test methods in a fixed order. Since the cognitive functioning of patients with IBD has not been fully previously investigated, the focus was on a wide range of neuropsychological functions. Global cognitive functioning was assessed by the Minimal Mental State Examination (MMSE). The MMSE contained 11 questions, subdivided into 5 subdomains. All questions were scored individually and added to produce a total score ranging from 0 to 30, with higher scores indicating better cognitive functioning[49]. The memory domain was evaluated with the Digit Span Forward and Backward subtests of, respectively the revised Wechsler Adult Intelligence Scale (WAIS-R)[50] and the revised Wechsler Memory Scale (WMS-R). Higher scores reflected better memory performance[51].

Executive functioning was assessed by the Word Fluency Test (WFT)[52], Stroop-Color-Word test (SCWT)[53] given in three parts, and the Trail Making Test (TMT)[54] subdivided into two parts, whereby part A measured attention and performance speed, and part B measured mental flexibility and ability to shift attention. The TMT involved scanning, visuomotor tracking, divided attention and cognitive flexibility. The time used for each trial was noted, with more time used indicating lower performance. The SCWT was used to measure interference sensibility. One response (reading the word) should be inhibited in order to name the colour of the ink, which leads to a delay in reaction time. The number of correct responses within 45 seconds was counted[53]. Furthermore, the WAIS-R Digit symbol and Digit cancellation test was measured[50].

Mental status: Cognitive performance depends on the psychiatric status of the patient[55], and therefore the Hospital Anxiety Depression Scale (HADS) was included in the neuropsychological examination. The HADS was used to determine depressive symptoms and anxiety. HADS is a widely used measurement to identify emotional disorders in non-psychiatric patients. The scale includes 14 items, 7 items concerning anxiety and 7 concerning depression, each scored between 0 and 3. A score above 8 on each individual scale were considered as a possible case and a score above 10 as a probable case[56].

QoL: To determine the QoL, the Short Form-36 (SF-36) was used. The SF-36 is a generic questionnaire to assess self-reported QoL. This measurement includes in total 8 subscales covering physical and mental aspects of QoL. The score ranges from 0 to 100, with higher score indicating better QoL. The Dutch translation of the SF-36 was validated in both the general population and in CD patients[57].

Statistical analysis

Data analyses were performed using SPSS 20.0, IBM Corp, 2011, Armonk, NY, United States. Descriptive statistics were used for the patients' characteristics. All comparisons between the patient and control groups were performed with an independent *t*-test. A *P*-value $\leqslant 0.05$ was considered statistically significant. To correct for multiple testing, the level of significance was set at $P < 0.01$ (0.05/5) and $P < 0.006$ (0.05/8) for the fatigue (five MFI subscores) and QoL (eight SF-38 subscales) scores, respectively. Based on the individual cognitive tests corrected for education, Z-scores of the different cognitive domains were created by using the UNIANOVA test with an average mean ± SD. Correlations between the MRI outcomes, cognition and mood status were performed with the Pearson Correlation test.

RESULTS

Demographic characteristics

In this study, 20 CD patients and 17 healthy controls were age ($P = 0.46$) and gender matched ($P = 0.68$). All patients were in clinical remission at study inclusion (mean HBI = 2.16, SD = 1.12), with an average age of onset at 21.4 years and an IBD disease duration of 8.8 years. Based on the inclusion criteria, patients reported more fatigue complaints according to the MFI-20 ($P < 0.001$) and VAS fatigue score ($P < 0.001$) compared with the control subjects. Furthermore, the education level of the healthy controls was significantly higher than that of the CD patients. Since this variable might influence mental status scores, a correction was made. An overview of the clinical characteristics of the individuals is presented in Table 1.

MRI analysis

Volumetric data: The comparison of the subcortical volumes between the CD patients and controls in the analysis of the T_1weighted images did not show significant differences between the two subject groups. The volume differences in the right amygdala ($P = 0.08$) and nucleus accumbens ($P = 0.08$) just missed significance (Table 2). VBM analysis showed a lower GM content in the superior frontal gyrus in CD patients compared with healthy controls ($P < 0.05$) (Figure 3).

MTI data: No significant differences were observed in the mean MTR values or in the MTR histogram peak heights of the CD patients compared with healthy controls.

MRS data: Lower glutamate + glutamine (Glx = Glu + Gln) concentrations (4.85 ± 0.78 mmol *vs* 5.96 ± 0.98 mmol, $P = 0.02$) and ratios to tCr (0.92 ± 0.13 *vs* 1.10 ± 0.14, $P = 0.02$) were found in the patient population compared with control subjects (Table 3).

ASL data: Average GM CBF of the CD patients (53.1 ± 6.1 mL/100 g/min) was significantly higher than the GM CBF of the control group (47.6 ± 8.6 mL/100 g/min) ($P = 0.05$).

DTI data: No differences were observed across white matter in the FA and MD values between CD patients and controls.

Mental status

Neuropsychological examination and cognitive scores were corrected for educational level (Table 4). Generally, a difference close to significance between patients and controls was found in several individual cognitive test scores. Compared with controls, CD patients had a lower Stroop interference index ($P = 0.06$), a reduced total score of the WAIS-R Digit

Table 1 Demographic characteristics

	CD patients (*n* = 20)	Controls (*n* = 17)	*P* value
Age (yr) at inclusion, mean ± SD	30.1 ± 6.2	28.5 (6.7)	0.460
Female, *n* (%)	17 (85.0)	13 (76.5)	0.680
HBI score, mean ± SD[1]	2.2 ± 1.1	-	-
Age of IBD onset (yr), mean ± SD	21.4 ± 5.7	-	-
IBD disease duration (yr), mean ± SD	8.8 ± 7.2	-	-
Smoker, *n* (%)	11 (55.0)	4.0 (23.5)	0.400
VAS, mean ± SD	7.4 (1.3)	3.4 (2.3)	< 0.001
MFI, mean ± SD	66.1 (13.3)	36.4 (10.3)	< 0.001
General Fatigue	16.4 (2.8)	8.9 (3.3)	< 0.001
Physical Fatigue	14.4 (3.0)	6.2 (2.2)	< 0.001
Mental Fatigue	12.8 (4.1)	7.2 (2.9)	< 0.001
Reduced Activity	10.7 (3.5)	6.9 (2.7)	< 0.001
Reduced Motivation	12.0 (3.6)	7.1 (2.7)	< 0.001
Education level, *n* (%)			0.001
Low[a]	4 (20)	-	
Intermediate[b]	10 (50)	2 (11.8)	
High[c]	6 (30)	15 (88.2)	
Montreal classification			
Location CD, *n* (%)			
L1 ileal	3 (15.0)	-	-
L2 colonic	2 (10.0)	-	-
L3 ileocolonic	15 (75.0)	-	-
L4 upper	-	-	-
L1-3 + L4	-	-	-
Behaviour CD, *n* (%)			
B1 non-stricturing/penetrating	15 (75.0)	-	-
B2 stricturing	3 (15.0)	-	-
B3 penetrating	2 (10.0)	-	-
+ Perianal disease	3 (15.0)	-	-
Medication use, *n* (%)			
Immunosuppressive drugs (Aza/6MP)	12 (60.0)	-	-
None	8 (40.0)	-	-

[1]HBI missing of 1 Crohn's disease (CD) patient. [a]Low: primary education (elementary school) and lower secondary education (preparatory secondary education); [b]Intermediate: higher secondary education (higher general continued education, pre-university secondary education) and postsecondary education (intermediate vocational education); [c]High: tertiary education (higher professional education, university). To correct for multiple testing, the level of significance was set at $P < 0.01$ for the MFI score. HBI: Harvey Bradshaw Index; VAS: Visual Analogue Scale; MFI: Multidimensional fatigue index.

Symbol test ($P = 0.06$) and were slower in completing trial A of the TMT test ($P = 0.08$). When the individual tests were transformed into a Z-score based on the different cognitive domains, significant reduced Z-scores of the memory domain ($P = 0.007$) and executive functioning domain ($P = 0.02$) were found in the patient population compared with the healthy controls (Table 5). CD patients experienced more depressive symptoms ($P < 0.001$), were more anxious ($P = 0.002$) and reported a significantly lower QoL.

Correlation of MRI findings with clinical characteristics and mental status

No correlations were found between mental status, including depression and anxiety, and MRI findings. Depressive symptoms were correlated with reduced scores of global cognitive functioning ($r = -0.5$, $P = 0.003$), memory ($r = -0.34$, $P = 0.04$) and executive functioning ($r = 0.35$, $P = 0.04$). Additionally, CD patients reported in the present study increased symptoms of anxiety and this was significantly correlated with reduced global cognitive functioning ($r = -0.36$, $P = 0.03$) and memory scores ($r = -0.32$, $P = 0.05$). No further correlations between cognitive scores, disease activity, disease duration and MRI findings were found in this study.

Table 2 Group mean subcortical structure volumes as percentage of the total brain volume in Crohn's disease patients and controls

	CD patients (*n* = 20)	Controls (*n* = 17)	*P* value
Left Accumbens	0.04 ± 0.01	0.04 ± 0.01	0.56
Left Amygdala	0.09 ± 0.01	0.09 ± 0.01	0.61
Left Caudate	0.24 ± 0.02	0.24 ± 0.02	0.94
Left Hippocampus	0.27 ± 0.02	0.27 ± 0.03	0.94
Left Pallidus	0.13 ± 0.01	0.12 ± 0.01	0.32
Left Putamen	0.33 ± 0.02	0.32 ± 0.03	0.24
Left Thalamus	0.54 ± 0.02	0.54 ± 0.03	0.94
Right Accumbens	0.04 ± 0.00	0.03 ± 0.01	0.08
Right Amygdala	0.08 ± 0.01	0.09 ± 0.01	0.08
Right Caudate	0.25 ± 0.03	0.25 ± 0.02	0.76
Right Hippocampus	0.26 ± 0.02	0.27 ± 0.03	0.22
Right Pallidus	0.12 ± 0.01	0.13 ± 0.01	0.30
Right Putamen	0.31 ± 0.08	0.32 ± 0.02	0.56
Right Thalamus	0.53 ± 0.02	0.52 ± 0.03	0.48

Mean in % ± SD. CD: Crohn's disease.

Table 3 Mean metabolite ratio to total creatine

	CD patients (*n* = 9)	Controls (*n* = 9)	*P* value
Ratio Glu:tCr	0.76 ± 0.12	0.84 ± 0.10	0.19
Ratio Cho:tCr	0.29 ± 0.02	0.29 ± 0.04	0.81
Ratio Ins:tCr	0.66 ± 0.08	0.70 ± 0.10	0.38
Ratio NAA:tCr	1.31 ± 0.12	1.27 ± 0.09	0.44
Ratio NAA + NAAG:tCr	1.59 ± 0.18	1.56 ± 0.13	0.69
Ratio Glu + Gln:tCr	0.92 ± 0.13	1.10 ± 0.14	0.02

Mean metabolite ratio to tCr in mmol ± SD. CD: Crohn's disease; tCr: Total Creatine; Glu: Glutamate; Cho: Choline; Ins: Insulin; NAA: N-Acetyl Aspartate; NAAG: N-Acetyl Aspartate Glutamate; Gln: Glutamine.

DISCUSSION

Several MRI techniques were used in this study in a cross-sectional manner to examine the differences in brain morphology, neurochemistry and perfusion between CD patients with fatigue and healthy controls without fatigue. The most important findings reported in this study are the significant differences in perfusion, neurochemistry and mental status (*e.g.*, cognition, mood and QoL) between patients and controls. Lower levels of Glx concentration and their ratio to tCr were observed and an increased CBF was found in the patient population compared with control subjects. CD patients scored lower on several individual cognitive

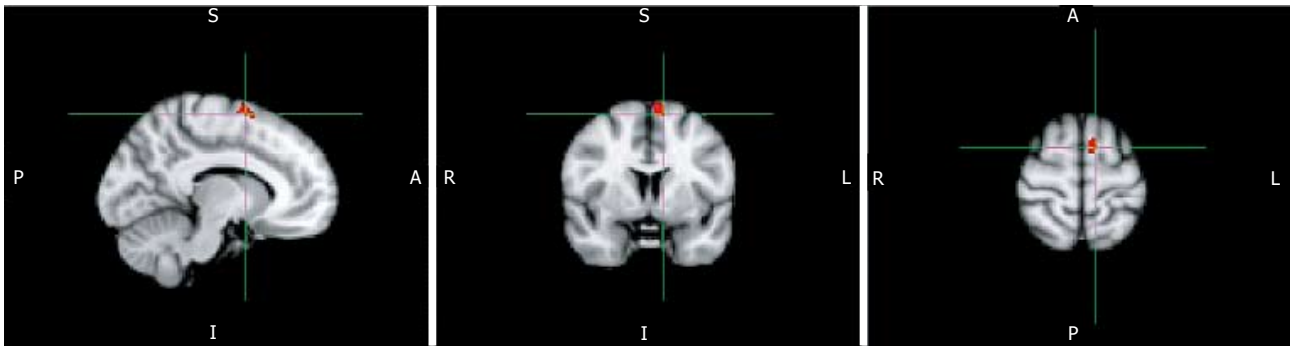

Figure 3 FMRIB Software Library voxel based morphometry analysis. Voxel based morphometry results shown on MNI152 standard space. The red colour indicates the voxels with significantly reduced grey matter volume in CD patients compared with healthy controls (with a *P*-value < 0.05, corrected for multiple comparison). The red voxels correspond to the left superior frontal gyrus.

test scores, with a trend towards significance, and scored significantly lower on the memory and the executive functioning domain compared with the healthy controls. Also, the patient population had a significantly lower QoL and mood status.

The present study observed with MRS a significantly reduced Glx concentration as well as a lower ratio of Glx to tCr in the CD group. Glutamate is the predominant excitatory neurotransmitter in the brain and is involved in different brain functions including memory and mood status. Receptors are mainly present in the hippocampus[58,59]. Glutamine is important in energy metabolism of the brain and previous studies reported that a reduced level of glutamine is associated with brain diseases such as Alzheimer[60,61]. Increasing evidence shows that major depression disorder is associated with altered function of the major excitatory and inhibitory neurotransmitters such as glutamate and GABA[62,63]. The present study did not find correlations between depressive symptoms and the reduced Glx concentration and ratio to tCr.

These reduced MRS results found in the present pilot study in CD patients are not in accordance with the findings of previous research performed in other inflammatory diseases such as RA and SLE[11,64]. RA and SLE patients were shown to have increased choline and myo-inisotol levels, indicating inflammation in the form of monocyte infiltration since this is a marker of cell membrane turnover[65,66]. In addition, in SLE patients only decreased NAA signals were reported, indicating neuronal loss[67-69], while an increased NAA ratio was found in our CD patient population. This contradiction may be due to the fact that RA and SLE are systemic inflammatory diseases, but not comparable with the systemic inflammation in IBD.

CBF values can reveal changes in tissue perfusion and are an indication for cerebral metabolism changes[70]. In the present study, significant higher CBF values were found in the patient population. Increased CBF is thought to be a compensatory mechanism in response to ischemia or injury, which could be the case in the CD patients due to inflammation[71,72]. Our findings are in line with the results of Wang *et al*[31] who described in their cohort that SLE patients had higher CBF values compared with healthy controls.

The volumetric results in this study extend on earlier findings in IBD patients. The reduced GM content of the superior frontal gyrus demonstrated in this study is in agreement with results presented by Agostini *et al*[73]. The superior frontal gyrus is involved the self-awareness, and important in processing information[74,75]. It has been suggested that the observed decrease in local GM volume could have many causes, including a decrease in cell size, neural or glial cell apoptosis or changes in blood flow[72]. It is not clear whether this local volume reduction is directly linked to systemic inflammation, but it may represent the anatomical substrate for the development of cognitive and emotional disturbances[73,76]. Similar significant positive correlations have been found between the GM volume in aging and measures of short-term memory[77].

Besides MRI findings, neuropsychological findings were assessed in this study. Previously, no evidence has been obtained on the association of the intrinsic disease process and cognitive dysfunction in IBD patients. It is probable that concurrent mood disorders, in particular depression, affect the cognitive performance of IBD patients in memory and executive functioning tasks[55]. This may be the case in the current cohort, since depressive symptoms were correlated with reduced neuropsychological scores in the three different domains: cognitive functioning, memory and executive functioning. However, Berrill *et al*[78] suggested that intellectual deficits existed in IBD patients compared to controls and remained significant after the correction for educational level and mood disorders.

Previous studies have shown a link between systemic inflammation and reduced brain volumes, possibly resulting in cognitive deficits. Zonis *et al*[79] suggested that chronic intestinal inflammation alters hippocampal neurogenesis and thus might underlie the behavioural manifestations in patients with IBD. In another study, SLE patients with cognitive deficits appeared to have reduced temporal lobe structures (hippocampus and amgydala) compared to SLE patients without cognitive

Table 4 Mental status

	CD patients (n = 20)	Controls (n = 17)	P value
Global cognitive functioning			
MMSE (total score), mean ± SD	28.9 (1.62)	29.65 (0.49)	0.87
Memory			
Verbal			
WMS memory quotient, mean ± SD[3]	109.2 (10.5)	115.7 (8.7)	0.72
Non verbal			
WMS visual reproduction (total score), mean ± SD[3]	11.6 (2.7)	12.9 (2.2)	0.75
WAIS-R Digit Span forward, mean ± SD	5.4 (1.0)	6.5 (1.3)	0.15
WAIS-R Digit Span backward, mean ± SD	4.5 (1.0)	5.2 (0.9)	0.15
Executive functioning			
WFT, mean ± SD[1]			
No. of good answers	42.7 (7.8)	48.2 (9.8)	0.29
No. of perseverative errors	0.28 (0.5)	0.47 (0.8)	0.58
Stroop Color-Word test, mean ± SD			
Stroop 1 time (s)	43.9 (7.2)	39.2 (8.6)	0.41
Stroop 1 No. of errors	0.2 (0.4)	0.1 (0.3)	0.98
Stroop 2 time (s)	56.6 (8.3)	53.8 (6.9)	0.62
Stroop 2 No. of errors	0.3 (0.8)	0 (0.0)	0.21
Stroop 3 time (s)	88.3 (14.7)	76.6 (8.8)	0.22
Stroop 3 No. of errors	0.6 (1.5)	0.13 (0.3)	0.20
Stroop interference index	50.1 (7.8)	56.1 (5.5)	0.06
TMT, mean ± SD			
Part A time (s)	30.3 (11.8)	22.1 (8.5)	0.08
Part A no. of errors	0.1 (0.2)	0.1 (0.2)	0.56
Part B time (s)	61.8 (29.2)	50.1 (17.4)	0.72
Part B no. of errors	0.1 (0.2)	0.2 (0.5)	0.41
WAIS-R Digit Symbol, mean ± SD[2]			
Total score	59.7 (8.4)	71.0 (6.2)	0.06
No. of errors	0 (0.0)	0.1 (0.3)	0.63
Digit cancellation test, mean ± SD[4]			
Total score	436.2 (88.1)	498.6 (82.9)	0.16
No. of good answers (%)	57.3 (29.5)	78.9 (20.9)	0.16
HADS, mean ± SD	13.1 (7.3)	4.8 (2.9)	< 0.001
Anxiety	7.5 (3.8)	3.7 (2.7)	0.002
Depression	6.1 (4.0)	0.9 (1.1)	< 0.001
SF-36			
Physical functioning	72.9 ± 20.2	96.6 ± 3.4	< 0.001
Social functioning	52.0 ± 29.0	90.7 ± 9.8	< 0.001
Role physical problem	71.3 ± 37.4	2.9 ± 8.3	< 0.001
Role emotional problem	40.4 ± 46.1	2.0 ± 8.1	0.002
Bodily pain	35.3 ± 20.7	5.6 ± 12.6	< 0.001
General health perception	65.8 ± 18.8	82.0 ± 15.2	< 0.001
Mental health	63.6 ± 16.0	80.4 ± 10.9	0.001
Vitality	30.1 ± 18.3	72.9 ± 14.3	< 0.001

[1]Missing in 2 CD patients; [2]Missing 1 CD patient and 1 healthy control; [3]Missing in 2 healthy controls; [4]Missing in 5 patients and 3 healthy controls. To correct for multiple testing, the level of significance was set at $P < 0.006$ for the SF-36 score. MMSE: Mini Mental State Examination; WMS: Wechsler Memory Scale; WAIS-R: Wechsler Adult Intelligence Scale-Revised; WFT: Word Fluency Test; TMT: Trial Making test; HADS: Hospital Anxiety Depression Scale; CD: Crohn's disease.

deficits[80]. In the present study, we did not find these correlations.

Some limitations of this study need to be revealed. Although this study is an exploratory study, the population size was limited. In this pilot study we have compared the most extreme cases; quiescent CD patients with fatigue *vs* healthy controls without fatigue. In this design, we have found significant differences between the groups and now further research is required. In addition, the significant difference in the fatigue score between patients and controls is not a finding of the study, but part of the design. As a consequence, it cannot be definitely concluded whether the differences in MRI measures are caused by CD per se or represent only patients with combined CD and fatigue. However, fatigue is a subjective measurement and was evaluated as such. It is hard to draw major conclusions from these questionnaires, since some healthy controls reported a high fatigue score as well due to other circumstances than IBD. In some MRI analyses, subjects got excluded due to the quality of the data. MRS data with high Cramer-Rao lower bounds, suggesting unreliable metabolite quantification, were excluded from data analysis. This could have been influenced by the patients' motion or bad shimming.

In conclusion, our findings support the hypothesis that systemic inflammation influences the brain and effects cognitive functioning and mood. This is a first step in the gathering of data and understanding of brain involvement in CD patients. This study implies that for a health professional, it is important to focus in CD patients not only on symptoms related to the gastrointestinal tract, but also on the effects of inflammation on the brain. Understanding these affects in CD patients may help health professionals to set up interventions to maintain CD remission by the use of medication and to improve mood status and QoL by *e.g.*, psychosocial interventions.

Table 5 Z-scores of the different domains of cognitive functioning

	CD patients (n = 20)	Controls (n = 17)	P value
Global cognitive functioning[1], mean ± SD	28.9 (1.6)	29.7 (0.5)	0.870
Memory[2], mean ± SD	1.1 (2.9)	1.3 (2.3)	0.007
Executive functioning[3], mean ± SD	2.5 (7.7)	2.9 (4.2)	0.020

[1]The global cognitive functioning domain includes the Minimal Mental State Examination; [2]The memory domain includes the Wechsler Adult Intelligence Scale and the revised Wechsler Memory Scale; [3]The executive functioning domain includes the Word Fluency Test, Stroop-Color-Word test and Trail Making Test. CD: Crohn's disease.

COMMENTS

Background

Both active and quiescent Crohn's disease (CD) is a chronic inflammatory status in which levels of circulating inflammatory cytokines, such as tumour necrosis factor-α are reported in the body. These cytokines may play a role in driving inflammation in the brain by activating microglia and the recruitment of monocytes.

Research frontiers

Metabolic and cerebral perfusion changes have been found in the brain of patients with other systemic diseases including rheumatoid arthritis, systemic

sclerosis and systemic lupus erythematosus. In addition, previous studies found an association with fatigue and metabolic brain changes. Thus it is of interest, whether systemic inflammation and fatigue complaints influence the brain in CD patients as well.

Innovations and breakthroughs

The present data support the hypothesis that systemic inflammation influences the brain and affects cognitive functioning and mood status in quiescent CD patients with fatigue. This is a first step in understanding brain involvement in CD patients.

Applications

This study implies that for a health professional, it is important to focus in CD patients also on the effects of inflammation on the brain. Understanding these affects in CD patients may help health professionals to set up interventions to maintain CD remission by the use of medication and to improve mood status and QoL by *e.g.,* psychosocial interventions.

Peer-review

Since this is an exploratory study, the authors have compared the most extreme cases; quiescent CD patients with fatigue *vs* healthy controls without fatigue. In this design, the authors have found significant differences between the groups and now further research is required.

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