No structural cerebral MRI changes related to fatigue in patients with primary Sjögren’s syndrome

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Abstract

Objective. Whether or not chronic fatigue is reflected in structural changes in the brain is a matter of debate. Primary SS (pSS) is characterized by dryness of the mouth and eyes, migrating muscle and joint pain and prominent fatigue. We aimed to investigate whether the severity of fatigue in pSS was associated with cerebral MRI findings.

Methods. Fatigue was measured with the fatigue visual analog scale in 65 patients with pSS. Global grey matter (GM) and white matter volumes were estimated from magnetic resonance T1 images, and associations between fatigue and brain volumes were assessed in regression models. Voxel-based morphometric analyses of GM were performed to investigate possible associations between fatigue and GM volume changes in particular brain regions.

Results. The fatigue scores in the patient group were spread across a wide range. Global volume analyses showed no significant effect of GM volumes and white matter volumes on fatigue. Voxel-wise analyses of GM did not identify any particular brain region associated with fatigue.

Conclusion. Fatigue is a dominant phenomenon in pSS patients but is not reflected in structural abnormalities in the brain as visualized by conventional MRI. Our findings support the hypothesis of fatigue as a physiological phenomenon that does not lead to vascular changes or neuronal or glial death or damage.

Key words: fatigue, primary Sjögren’s syndrome, voxel-based morphometry, MRI, brain, imaging

Introduction

Chronic fatigue—a condition characterized by an ‘overwhelming sense of tiredness, lack of energy and feeling of exhaustion’ [1]—is a phenomenon experienced by many patients who suffer from chronic inflammatory or infectious diseases, as well as non-inflammatory conditions such as neurodegenerative diseases and cancer. The severity and consequences of fatigue can be considerable, as can the impact on normal daily function [2–4].

Although pain, depression and sleep disorder are important contributors to fatigue, they do not fully explain or predict the severity of fatigue [5–7], suggesting the existence of other factors that generate and...
regulate fatigue, which require further exploration [8–10]. A relevant hypothesis is that chronic fatigue in humans has similarities to sickness behaviour in animals, an evolutionary deeply conserved survival mechanism. This automated and unconscious behaviour is signalled through pro-inflammatory cytokines that act on the brain [11–14]. Sickness behaviour, and consequently fatigue, can be regarded as a normal and physiological phenomenon, and we hypothesized that molecular pathways and neuronal signalling of fatigue will not result in damage to neurons, glial cells or brain vasculature. Consequently, no structural abnormalities would be expected to be evident on conventional cerebral MRI. Previous studies of fatigue in SLE, chronic fatigue syndrome, multiple sclerosis (MS) and AS have not revealed consistent findings, but in some studies grey matter (GM) and/or white matter (WM) atrophy and increased WM hyperintensities (WMHs) and lower fractional anisotropy of WM tracts have been described [15–25].

Primary SS (pSS) is a chronic autoimmune disease that mainly affects exocrine glands, leading to dryness of the mouth and eyes. A majority of patients also have general symptoms and complaints, such as migrating joint and muscle pain, malaise and fatigue, which is one of the most prevalent and bothersome phenomena [3, 5, 26]. To investigate the mechanisms of chronic fatigue further, we performed a cerebral MRI study to explore whether fatigue in patients with pSS is associated with changes in brain volumes. Secondarily, we analysed associations between fatigue and WMHs.

Method
Subjects
The identification and inclusion procedure for participants in this study has previously been described in detail [27]. In brief, 72 (73%) out of 99 patients fulfilling the American European Consensus Group Criteria for pSS [28] provided informed written consent to participate. Two patients were ineligible for MRI examination because of cochlear implants or claustrophobia, three patients were excluded after visual inspection of the MRI scans because of poor image quality, and two patients were excluded because of missing MRI scans. Thus, 65 patients remained eligible for analysis. Selected demographic and clinical characteristics are presented in Table 1.

Hypertension was defined as systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg and/or receiving anti-hypertensive therapy at the time of examination. Fatigue was assessed by the fatigue visual analog scale (fVAS), which is a generic fatigue instrument that has been widely used to measure fatigue in patients with pSS and other diseases [29]. The fVAS uses a 100-mm line with vertical anchoring lines with the phrases ‘no fatigue’ at the left end (0 mm) and ‘worst possible fatigue’ at the right end (100 mm). Patients were asked to rate their level of fatigue in the last week by placing a marker at a point along the line that best corresponded to their perception of fatigue. The fVAS instrument is simple to use and shows good response to change over time.

Haematological, biochemical and immunological tests were performed in the hospital’s laboratory. The study was approved by the Regional Committee for Medical Research Ethics in Norway (REK vest 2010/1455) and was carried out in compliance with the Declaration of Helsinki.

MRI scan protocol
For research purposes only, patients were examined using a 1.5 T Philips Gyroscan NT Intera Release 10 (Philips Medical Systems, Best, The Netherlands). MRI data from patients were collected non-contiguously using the following protocol: axial T2 turbo spin echo (SE) with repetition time (TR) 3240 ms, echo time (TE) 19 ms/80 ms, slice thickness 5 mm, gap 1.5 mm; sagittal T2 fluid-attenuated inversion recovery with TR 6500 ms, inversion recovery 2200 ms, TE 105 ms, slice thickness 5 mm and gap 1 mm. Axial T1 three-dimensional turbo field echo with TR 17 ms, TE 4 ms, no gap; field of view 230 mm × 230 mm, matrix 256 × 256, nominal resolution 0.9 mm × 0.9 mm × 1.4 mm; axial T1 SE with TR 525 ms, TE 12 ms, slice thickness 5 mm, no gap, performed before and after administration of gadolinium-containing contrast agent in a cubital vein; and sagittal T1 SE with TR 525 ms, TE 12 ms, slice thickness 5 mm and no gap. For the image analyses, the axial T1 three-dimensional turbo field echo images with nominal resolution 0.9 mm × 0.9 mm × 1.4 mm were used. WMHs were graded according to Scheltens’ scale [30], and cerebral infarcts were assessed as previously described in detail [31].

MRI data processing
MRI images were pre-processed using default settings in the VBM8 extension (Gaser, http://www.neuro.

TABLE 1 Selected demographic and clinical characteristics of patients with primary SS

| Characteristics                        | (n = 65) |
|----------------------------------------|----------|
| Age, median (range), years             | 58.1 (27.1–79.1) |
| Females, n (%)                         | 56 (86.2) |
| Disease duration, median (IQR), years  | 6.9 (3.1–11.1) |
| No. of AECG criteria fulfilled, median (range) | 5 (3–6) |
| MSG focus score ≥1, n (%)              | 51 (78.5) |
| Anti-SSA antibodies, n (%)             | 50 (76.9) |
| Anti-SSB antibodies, n (%)             | 30 (46.2) |
| Fatigue VAS score, median (IQR)        | 65 (37–76) |
| Fatigue VAS score, range               | 3–93     |
| Hypertension, n (%)                    | 40 (61.5) |

AECG: American European Consensus Group (criteria for pSS) [28]; IQR: interquartile range; MSG: minor salivary glands; pSS: primary SS; SSA: SS-related antigen A; SSB: SS-related antigen B; VAS: visual analog scale.
uni-jena.de/vbm/download/) of the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The data processing is illustrated in Fig. 1. First, the images were bias corrected and the tissue classified as GM, WM and cerebrospinal fluid. The segmentation of GM and WM was visually analysed for all study participants. Segmented GM images were registered by using linear and non-linear transformations within a unified model [32]. After the normalization step, images were modulated by multiplying the Jacobian determinants from the normalization step to preserve individual GM volumetric differences within a common standard template. The normalization included correction for individual brain size. Finally, the images were smoothed using a 12-mm full-width-at-half-maximum Gaussian kernel to reduce the inter-subject variability and yield a more normal distribution of the data [33]. Data quality and sample homogeneity were tested by viewing one normalized unsegmented slice for all patients and evaluating a covariance matrix of the covariance among all volumes using the VBM8 tool (Gaser, http://dbm.neuro.uni-jena.de/vbm/download/). Global GM and WM volumes for each individual were estimated with the VBM8 tool using the modulated normalized images.

Identification of specific regions for voxel-wise analyses was done within selected masks defined by applying WFU PickAtlas version 3.0.4 (http://www.nitrc.org/projects/wfu_pickatlas/) [15, 34, 35]. The atlases chosen were as follows: TD Brodmann areas for substantia nigra and hypothalamus; TD lobes for midbrain, pons, frontal lobe and parietal lobe; and aal for thalamus (Thalamus L and Thalamus R) and caudate (Caudate L and Caudate R). All voxels with <10% probability of being GM were excluded to avoid possible edge effects between different tissue types.

**Statistical analyses**

The associations between fatigue and brain volumes were assessed in univariable and multivariable linear regression models using IBM SPSS Statistics 23 (IBM Corp., Armonk, NY, USA). Age, sex, disease duration and hypertension were included as potential confounders in the multivariable models. We present estimated effects with confidence intervals, *P*-values from tests of null effects and changes in $R^2$ from inclusion of the individual brain volume measures. Similarly unadjusted and adjusted effects of WMHs were estimated in separate analyses, including age, sex, disease duration and hypertension as potential confounders.

To explore regional changes in GM volume associated with fatigue scores, we performed multivariable linear regression analysis voxel-wise by applying the SPM8 software. We used false discovery rate correction for multiple testing, with a significance threshold $q < 0.05$. To reduce the risk of missing relevant areas because of the amount of corrections, the primary analyses were limited to regions that had previously been reported to have abnormal MRI findings associated with fatigue in other disease groups, specifically MS and chronic fatigue syndrome [16, 17, 36–38]. The regions examined were the midbrain, pons, hypothalamus, frontal lobe, caudate, thalamus, parietal lobe and substantia nigra. Further explorative analyses of the whole brain were performed to identify other areas that could be relevant for fatigue.

**Fig. 1** Flow diagram of the pre-processing steps for global volume and voxel-based morphometry analyses

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CSF: cerebrospinal fluid; GM: grey matter; WM: white matter.
Results

Fatigue and global brain volumes

Descriptive data for fatigue scores, GM and WM volumes for the 65 pSS patients are presented in Tables 1 and 2 and illustrated in Fig. 2. GM and WM volumes were plotted against the fVAS scores (Fig. 3), disclosing no discernible patterns. Multivariable regression analyses showed no association between fatigue and global GM volume or between fatigue and WM volume (Table 3).

Fatigue and regional brain volume changes

No association between fVAS scores and GM volume changes was revealed by voxel-wise analyses in either the analyses of the specific regions of interest or in the whole brain analysis of the 65 patients.

Fatigue and WMHs

The unadjusted effects of WMH scores showed no clear associations with fVAS scores. When correcting for age, sex, disease duration and hypertension in the regression model, higher scores of WMHs were significantly associated with increasing fatigue (Table 3).

Discussion

We found no structural brain abnormalities by conventional cerebral MRI related to the severity of fatigue in

Table 2 MRI findings in the patient group (n = 65)

| Parameters assessed                                      | Median (IQR)             | Range       |
|----------------------------------------------------------|--------------------------|-------------|
| From voxel-based morphometry                              |                          |             |
| GM volume, cm³                                           | 540 (519–561)            | (426–703)   |
| WM volume, cm³                                           | 529 (497–583)            | (420–688)   |
| CSF volume, cm³                                          | 277 (261–301)            | (208–366)   |
| Total brain volume, cm³                                   | 1347 (1281–1434)         | (1105–1638) |
| From radiological assessmenta                            | No. of patients          | Median (range) |
| Cortical infarcts                                         | 0/65                     | 0 (0–1)     |
| Lacunar infarcts                                          | 1/65                     |             |
| WMHs, Scheltens’ scale                                    | 52/64b                   | 3 (0–28)    |

aAll scans were rated by two experienced radiologists in a blinded manner.
bWMH data were missing for one patient.

CSF: cerebrospinal fluid; GM: grey matter; IQR: interquartile range; WM: white matter; WMHs: white matter hyperintensities.

Fig. 2 Distribution of grey matter and white matter volumes and fatigue visual analog scale scores in 65 primary SS patients

GM and WM volumes (in centimetres cubed) were calculated from VBM8. fVAS: fatigue visual analog scale; GM: grey matter; pSS: primary SS; VBM: voxel-based morphometry; VBM8: software extension to SPM8 software; WM: white matter.
Fig. 3 Association between fatigue and brain volumes in 65 primary SS patients

Scatter plots illustrating the association between fVAS scores with GM and WM volumes from VBM analyses. fVAS: fatigue visual analog scale; GM: grey matter; VBM: voxel-based morphometry; WM: white matter.
patients with pSS. This result applies to global GM and WM volume differences, as well as to regional GM volume differences from voxel-wise analyses. WMHs were associated with fatigue score, but the effect size was too small ($R^2 = 0.074$) to imply any biological significance. Our findings are in agreement with the hypothesis of fatigue as a physiological phenomenon.

A number of studies in various diseases have reached different conclusions regarding these matters. Several studies in MS have shown associations between cerebral MRI abnormalities and fatigue [23, 39–41]. One study in MS did not, however, reveal differences in global brain damage between patients with or without fatigue, although there were differences in regional brain damage [23]. Additionally, a study by Codella et al. [42] concluded that structural pathology of the GM did not play a large role in the development of fatigue in MS patients. Furthermore, Biberacher et al. [43] did not confirm any significant association between fatigue and structural brain changes in MS patients but suggested that such associations might be proved by other MRI methods. In MS, both neurons and glial cells are subjected to more or less severe inflammation and destruction. Thus, correlations between structural changes in the brain and fatigue are to be expected if the latter is also affected by disease activity, even if no causal pathways are involved. Assessment of possible causal links between structural brain changes and fatigue is better done among individuals with conditions in which no disease processes take place in the brain itself, as opposed to MS neurodegenerative diseases and post-stroke conditions.

**WM damage and fatigue**

The WMH load in patients with SLE in relationship to fatigue has previously been studied by our group, showing that increased WMH load is associated with more severe fatigue [24]. This was not the case in patients with pSS; a finding that is also supported by our previous study identifying no differences in lesion load between pSS patients and healthy subjects [31].

Granulomatosis with polyangiitis is, like pSS, a disease that usually has no involvement of the brain. Basu et al. [19] studied possible associations between brain MRI findings and fatigue in this disease and found no evidence for significant differences in WMHs between patients with chronic fatigue and patients without fatigue. Studies of lesion volume in MS patients showed no differences between patients with and without fatigue [21, 44]. In contrast, a recent study of patients with AS found that high fatigue scores were correlated with lower fractional anisotropy, suggesting WM tract damage, and hypothesized that fatigue could affect WM independently of GM abnormalities [25]. Furthermore, microstructural changes demonstrated by diffusion tensor imaging have been associated with chronic fatigue in some studies of MS granulomatosis with polyangiitis and FM. Both decreased and increased fractional anisotropy were reported in specific regions of the brain [19, 23, 37, 45, 46]. One study found decreased fractional anisotropy in MS patients compared with controls but failed to find any correlation with fatigue score [42]. Diffusion tensor imaging is preferred over voxel-based morphometry (VBM) for analysing WM.

**Other imaging methods**

Some functional MRI (fMRI) studies support associations between fatigue and functional neuronal activity in the brain. Changes in brain activity in the striatum and the cerebellar, temporal, cingulate and frontal regions have been reported in patients with MS chronic fatigue syndrome and vasculitis [37, 38, 47, 48]. The fMRI modality is a promising tool for further investigation of cerebral fatigue processes.

**Strengths and limitations**

We cannot exclude shortcomings from the lack of power in our study. There is a risk that the regions chosen for VBM analyses are not optimal in pSS because they were chosen based on studies of MS. Another limitation is that the imaging methods applied are not sensitive
enough for detecting microstructural changes in WM. Furthermore, we found that the GM volumes had a peaked distribution within the data range; thus, the small variation in GM volumes does not explain the wider variation of VAS scores, as shown in Fig. 2. Also, our findings apply to conventional MRI methods only.

Strengths of the study are the relatively large and homogeneous cohort of patients fulfilling the classification criteria for pSS, near population-based retrieval, standardized examination and a disease (pSS) that does not involve damage to brain tissue. In addition, validated methods for VBM analyses, fatigue scoring and correction for multiple testing have been used.

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