

Fatigue and Regulation of the Hypothalamo-Pituitary-Adrenal Axis in Multiple Sclerosis

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Background: Fatigue is a common and disabling symptom in patients with multiple sclerosis (MS). Underlying mechanisms postulated so far have involved localization of brain lesions and abnormalities of the neuroendocrine system and cytokine regulation.

Objective: To investigate the relationship between fatigue and the hypothalamo-pituitary-adrenal (HPA) axis in patients with MS.

Design: A prospective survey.

Setting: Outpatient and inpatient study at the Max Planck Institute of Psychiatry, Munich, Germany.

Patients: Thirty-one patients with clinically definite MS, a relapsing-remitting disease course, and without MS-specific treatment.

Interventions: Assessment of fatigue with 3 questionnaires: the Fatigue Severity Scale (FSS), the Modified Fa-

tigue Impact Scale (MFIS), and the Visual Analog Scale. Assessment of HPA axis regulation with the combined dexamethasone–corticotropin releasing hormone (Dex-CRH) test.

Results: The FSS score was significantly correlated with the MFIS score. Patients with fatigue had significantly elevated adrenocorticotropin (ACTH) levels in the combined Dex-CRH test.

Conclusions: In contrast to results for chronic fatigue syndrome, where a hyporeactivity of the HPA axis has been shown, MS patients with fatigue exhibited a higher activity of the HPA axis than those without fatigue, as evidenced by significantly increased ACTH concentrations. Proinflammatory cytokines, known to be elevated in patients with MS, may cause both HPA axis alterations and fatigue.

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FATIGUE IS AN OVERWHELMING sense of physical tiredness and lack of energy distinct from sadness and weakness.¹ It is a physiologic phenomenon preceding sleep, but it also occurs as a disabling symptom in many patients with multiple sclerosis (MS), most frequently in the early stages of the disease. Although fatigue is common among patients with MS, evaluation of this symptom is difficult because of the subjectivity and variability of the complaints. As a result, many subjective fatigue scales have been developed, and trials have been conducted to measure fatigue quantitatively in terms of muscle strength.²

The pathophysiologic characteristics of fatigue are poorly understood. There is some evidence that peripheral abnormalities such as alterations in muscle metabolism contribute to fatigue in patients with

MS.^{2,3} It has been suggested that abnormalities in the central nervous system (CNS) may play an important role in the pathogenesis of fatigue in MS.⁴ Inflammatory mediators such as cytokines in the CNS⁵ or localized damage to specific neuroanatomic regions⁶ may be the cause. And some investigators have provided evidence that pyramidal tract abnormalities are associated with fatigue in MS.^{2,7}

There is strong evidence in both human and animal studies that MS is an autoimmune disease driven by autoreactive T cells and characterized by an imbalance of proinflammatory T helper (Th) 1 cytokines (eg, tumor necrosis factor α , interferon gamma, interleukin [IL] 2, and lymphotoxin)^{8,9} and regulatory Th2 cytokines (eg, IL-4 and IL-10).^{10,11} Because of the background of the interplay of the immune and endocrine systems, the hypothalamo-pituitary-adrenal (HPA) axis has been studied in patients with MS.¹² Sev-

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eral investigations suggest a hyperreactivity of the HPA axis in MS related to the clinical course, which might be caused by the well-known elevation of proinflammatory cytokine levels.¹²⁻¹⁴ In contrast, several studies on the relationship between the chronic fatigue syndrome (CFS) and the HPA axis have demonstrated a hyporeactivity of the HPA axis in patients with this disorder.¹⁵ The present study was performed to investigate the association between fatigue and HPA-axis activity in patients with MS.

METHODS

PATIENTS

Thirty-one patients with clinically definite MS according to the criteria of Poser et al¹⁶ and a relapsing-remitting disease course were recruited from the outpatient and inpatient units of the hospital. The patients had been without glucocorticoid treatment for at least 4 weeks. Of the 31 patients, 25 had never had any immunosuppressive or immunomodulatory treatment. Four patients had received treatment with azathioprine, 1 with interferon beta, and 1 with interferon beta and mitoxantrone, all years earlier. None of the patients had taken any centrally acting medications such as antidepressants in the last several years. Patients diagnosed as having a major depressive disorder, those who had a score above 14 on the Hamilton Depression Rating Scale,¹⁷ and those with another severe medical disorder were excluded from the study. Written informed consent was obtained from all subjects prior to the investigation.

CLINICAL ASSESSMENT

Subjects were interviewed, and then they completed several standardized self-report fatigue questionnaires: the Fatigue Severity Scale (FSS) of Krupp et al,¹⁸ the Modified Fatigue Impact Scale (MFIS) of the Multiple Sclerosis Council,¹⁹ and the visual analog scale (VAS).¹⁹ A neurologic examination was performed, and the patient's neurologic disability was assessed using the Kurtzke²⁰ Expanded Disability Status Scale (EDSS).

THE Dex-CRH TEST AND DETERMINATION OF PLASMA HORMONE CONCENTRATIONS

The HPA axis activity was assessed with the combined dexamethasone-corticotropin releasing hormone (Dex-CRH) test on the day the patient completed the questionnaires. The test was performed as described previously.¹³

Blood was drawn into prechilled tubes containing EDTA and aprotinin and centrifuged. The plasma was stored at -80°C until measurement. Cortisol and adrenocorticotropin (ACTH) concentrations were determined using commercial radioimmunoassay (Immun Chem Cortisol; ICN Biomedicals, Costa Mesa, Calif; and RIA-ACTH; Nichols Institute Diagnostics, San Juan Capistrano, Calif) with an interassay variation coefficient of less than 8% and an intra-assay variation coefficient of less than 4%.

DATA ANALYSIS

The patients were divided into 2 groups by FSS scores: the fatigue group had FSS scores of 4.0 or higher; the nonfatigue group had FSS scores lower than 4.0. The following variables were calculated: For the Dex-CRH test: maximum rise (deltamax) in levels of cortisol and ACTH after human corticotropin-

releasing hormone injections; area under the curve (AUC) from 3 to 4:15 PM using the trapezoidal rule; and the mean location of the curve (ML). Differences in the variables deltamax cortisol, AUC cortisol, ML cortisol, deltamax ACTH, AUC ACTH, and ML ACTH between the 2 groups were tested for significance by means of a 1-factorial multivariate analysis of covariance, with sex, age, and EDSS score as covariates. As the nominal level of significance, $P < .05$ was accepted. In case of a significant factor effect, univariate F tests were performed to identify the variables contributing significantly to this effect. These tests were performed with a reduced level of significance (Bonferroni correction) to keep the type I error to .05 or lower. Data are given as mean \pm SEM or median and range. Pearson r was used to assess the relationship between different fatigue scales.

RESULTS

Of the 31 patients studied with clinically definite MS and a relapsing-remitting disease course, 15 (48%) were assigned to the fatigue group and 16 to the nonfatigue group. Aside from fatigue, the groups had comparable clinical characteristics. The fatigue group consisted of 12 women and 3 men (mean \pm SEM age, 39.60 ± 1.84 years) and the nonfatigue group of 10 women and 6 men (mean \pm SEM age, 32.38 ± 2.62 years). The median EDSS score was 1.5 (range, 1.0-4.5) in the fatigue group and 2.0 (range, 0.0-6.5) in the nonfatigue group. Age at onset was similar in the 2 groups (fatigue group, 28.73 ± 2.26 years; nonfatigue group, 28.88 ± 1.82 years).

Of the 31 patients, 15 had a fatigue score of 4 or higher on the FSS, indicating fatigue (mean \pm SEM FSS scores: fatigue group, 5.27 ± 0.20 ; nonfatigue group, 2.72 ± 0.23). The FSS score was highly significantly correlated ($P < .001$; Pearson $r = 0.65$) with the MFIS score (MFIS scores: fatigue group, 1.91 ± 0.13 ; nonfatigue group, 1.40 ± 0.28). In contrast, it was not correlated with the severity of fatigue as measured by the VAS (VAS scores: fatigue group, 0.58 ± 0.05 ; nonfatigue group, 0.66 ± 0.37). But the VAS and MFIS scores had a significant correlation ($P < .001$; Pearson $r = 0.51$).

There was a significant effect of fatigue on the HPA axis activity ($P < .03$, Wilks multivariate tests of significance). The patients with fatigue had significantly increased ACTH levels compared with those without fatigue (univariate F tests, $P < .05$; **Figure, A**). However, their cortisol levels were not significantly elevated (**Figure, B**). None of the covariates age, sex, EDSS score, or duration of disease were found to have influence on fatigue.

COMMENT

Fatigue is a common symptom in MS and is reported by more than one third of patients.^{1,21,22} Using the FSS, we found that 48% of our patients experienced fatigue. The FSS is the most widely accepted unidimensional scale.¹⁸ Multidimensional assessment of fatigue is possible with the MFIS,¹⁹ which showed a highly significant correlation with the FSS in our study. In line with recently published results,²³ the VAS was less powerful in detecting fatigue in patients with MS. We found no correlation be-

tween fatigue and neurologic disability as determined with the EDSS in our study population, which is in line with several other publications.^{21,22,24} This reflects the observation that fatigue often occurs in the early stages of the disease and is often the leading symptom despite a low EDSS score. However, other investigators have reported an association between physical disability and fatigue.²⁵⁻²⁷ Fatigue was independent of age, sex, and duration of disease.

In our study, the MS patients with fatigue showed a dysregulation of the HPA axis, as demonstrated by significantly elevated plasma ACTH levels. In contrast, Heesen et al²⁸ recently found no correlation between fatigue and HPA axis activity in 40 patients with MS. A possible explanation is differences between the MS populations studied: Heesen et al investigated 32 patients with a chronic progressive course and 8 with a relapsing-remitting course. In support of our findings, several studies have shown correlations between HPA axis function and both disease activity and course of disease. Patients with a chronic progressive MS course showed increasing HPA axis activity.¹²⁻¹⁴ Another reason why the findings are inconsistent may be that the study population of Heesen et al²⁸ received immunomodulatory and immunosuppressive agents such as interferons, glatiramer acetate, methotrexate, and mitoxantrone, whereas patients being treated with such medications were excluded from other studies, including ours, because some of these therapies influence cytokines, which have an effect on HPA axis activity.^{29,30} Furthermore, Heesen et al²⁸ did not divide patients into subgroups with and without fatigue as we did, and fatigue as determined by the FSS was lower than in our group.

In contrast to our study, which demonstrates a hyperreactivity of the HPA axis in MS patients with fatigue, several studies of non-MS patients with CFS showed a hyporeactivity.¹⁵ Our patients with MS had fatigue scores similar to those of the patients with CFS. However, in 1 study, non-MS patients with CFS had significantly higher somatization scores than patients with MS, which reflects strong focusing on bodily sensations.²² Patients with MS are more likely than healthy individuals to report that their fatigue is easily triggered, worsened by heat, and that it prevents sustained physical functioning.²¹ Therefore, CFS seems to be different from fatigue in MS both clinically and with respect to HPA axis activation.

Immune activation is known to be elevated in patients with MS, and the proinflammatory cytokines involved may be the cause of the HPA axis alterations and a strong feeling of fatigue in patients with MS. Studies in patients and animals with MS found an association between fatigue and some proinflammatory cytokines, including tumor necrosis factor α and IL-1,^{5,31,32} which are known to activate the HPA axis. Increased serum levels of IL-1 affect the hypothalamus and cause fever, fatigue, and myalgia.³³ Other markers, including urinary neopterin excretion (a marker of interferon gamma-activated macrophage activity) and excretion levels of serum C-reactive protein (CRP) and soluble intercellular adhesion molecule-1, showed no significant association with fatigue in MS.³⁴ However, in 1 study, patients with higher CRP levels had higher FSS scores, which corre-

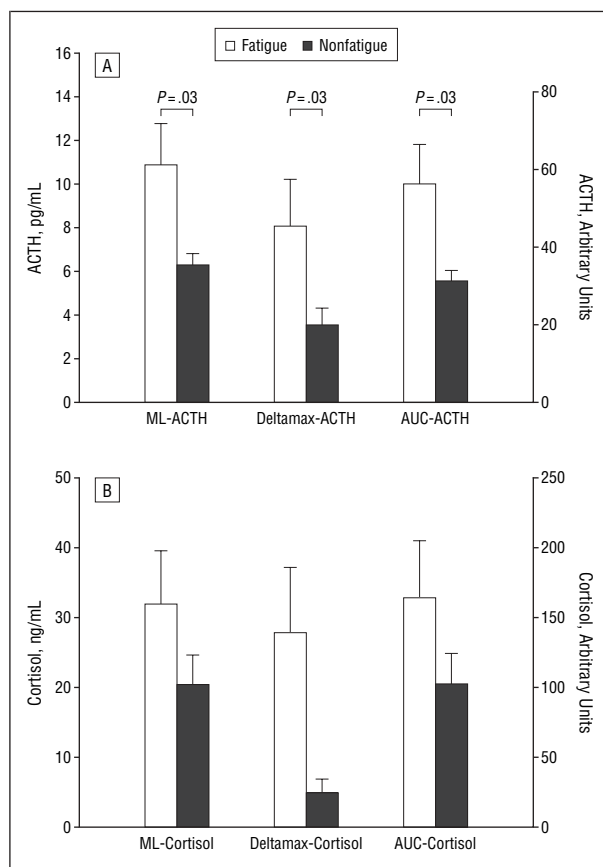


Figure. Reactivity of the hypothalamo-pituitary-adrenal axis in multiple sclerosis patients with and without fatigue. A, Adrenocorticotropic (ACTH) levels were significantly higher in the patients with fatigue than in those without fatigue. B, Cortisol levels did not differ statistically between patients with and without fatigue. Error bars indicate standard error of the mean; AUC, area under the curve; deltamax, greatest increase; and ML, mean location of the curve.

lated with a more severe course of disease.³⁴ Wei and Lightman¹⁴ found higher CRP levels in MS patients with a hyperreactivity of the HPA axis.¹⁴ C-reactive protein is induced by IL-6, which is known to be a strong activator of the HPA axis.³⁵ Flachenecker et al³⁶ found significantly higher median levels of tumor necrosis factor α messenger RNA expression in MS patients with fatigue than in those without fatigue. In 1 study, aspirin caused a reduction in fatigue severity in patients with MS.³⁷

Taken together, these findings support the hypothesis of an association between proinflammatory cytokines and both fatigue and up-regulation of the HPA axis in patients with MS, and we postulate that cytokine-induced impairment of corticoid receptor signaling accounts for this effect.³⁸ We further postulate that successful reinstatement of corticosteroid receptor function by appropriate drugs such as antidepressants will have a positive influence on both MS-associated HPA axis dysfunction and fatigue.^{39,40}

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