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Circadian cortisol, depressive symptoms and neurological impairment in early multiple sclerosis

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Summary
Objective: There is evidence for the existence of a hyperactive hypothalamus—pituitary—adrenal (HPA) axis and its potential role in disease progression in multiple sclerosis (MS). Depressive symptoms are also common in MS. At the same time, depressive symptoms are often associated with an elevated circadian cortisol secretion. So far, little is known about the interplay between depressive symptoms and circadian HPA axis abnormalities in MS.
Methods: Here we investigated depressive symptoms, circadian HPA axis function, cortisol awakening response (CAR) and neurological impairment in 32 early stage relapsing-remitting MS (RRMS) patients and 16 age- and sex-matched controls. Saliva cortisol samples were collected in patients' home environment. Depressive symptoms were assessed by self-report measures. Neurological impairment was assessed by the Kurtzke Expanded Disability Status Scale (EDSS).
Results: RRMS patients expressed a significantly higher CAR when compared to healthy controls. After patients were divided into two groups based on their depressive symptom load (Beck Depression Inventory (BDI); median-split), only RRMS patients with moderately elevated depression scores (BDI high) statistically differed in their cortisol release when compared to healthy controls. RRMS patients with low depression scores (BDI low) expressed similar circadian patterns as healthy controls. Neurological impairment (EDSS) was more pronounced in the BDI high group than in the BDI low group.
Conclusion: In summary, there is evidence, that a hyperactive HPA axis is primarily present in MS patients expressing moderately elevated depressive symptoms. MS patients with only few depressive symptoms do not significantly differ in CAR when compared to healthy controls. To the best of our knowledge, this is the first study showing that in early stage MS, a hyperactive HPA axis is primarily present in patients who express moderate depressive symptoms.

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1. Introduction

Multiple sclerosis (MS) is an autoimmune-mediated demyelinating disease of the central nervous system. It is characterized by an unpredictable, often progressive course and various symptoms of neurological disability. In the initial phase of the disease, the majority of patients are characterized by repeated relapses in neurological symptoms with complete or incomplete remissions (relapsing remitting MS (RRMS)). In RRMS, no progression in disability is observed in the absence of an acute relapse. In contrast, progressive courses are defined by a continuous progression in disability in the absence of any acute relapse (primary progressive MS/PPMS) or in between two or more relapses (secondary progressive MS/SPMS). Common symptoms are impaired motor function, visual problems, sensory disturbances, bowl and bladder dysfunction as well as cognitive impairment. Psychiatric co-morbidity such as depression and anxiety is also often reported (Compston and Coles, 2002). MS is regarded the most common neurological disorder in young adults and is associated with progressive neurological impairment and a significant decrease in quality of life (Amato et al., 2001).

While the precise pathogenesis of MS is still poorly understood, stress and dysregulation of the hypothalamus—pituitary—adrenal axis (HPA axis) have been previously identified as potential modulating factors (Gold et al., 2005a; Heesen et al., 2007).

In a very comprehensive clinical study on 173 MS patients, elevated plasma and 24 h-urinary cortisol levels in RRMS patients were reported (Ysrraelit et al., 2008).

Several studies investigated HPA axis function in response to pharmacological stimulation such as the dexamethasone/corticotropin releasing hormone (CRH) test: In response to intra-venous administration of CRH, cortisol release was increased in acute RRMS or chronically progressive MS patients compared to age and sex matched healthy controls (Grasser et al., 1996; Then Bergh et al., 1999). RRMS patients expressed moderate elevations, while patients with a secondary progressive or primary progressive course showed intermediate to pronounced elevations in cortisol (Then Bergh et al., 1999).

At the same time, HPA axis abnormalities in MS seem to be linked to clinical aspects: In a three year follow-up study, Gold et al. (2005b) found evidence that a high ACTH response after CRH administration was associated with disease progression (e.g. increase in neurological disability) as well as cognitive dysfunction.

In a sample of 23 acute RRMS patients, CRH administration resulted in an elevated cortisol release when compared to healthy controls. Maximum cortisol levels correlated with physician's depression ratings but not with self-reported depressive symptoms. Patients with significantly increased cerebrospinal fluid (CSF) cell counts showed significantly higher scores on the Hamilton rating scale for depression. CSF cell count also correlated with maximum cortisol release in the CRH test (Fassbender et al., 1998).

A hyperactive HPA axis has also been described in depressive disorders (Ehlert et al., 2001; Vreeburg et al., 2009; Weinstein et al., 2010; Wichers et al., 2008). Large cohort studies (Vreeburg et al., 2009) as well as twin-studies (Vinberg et al., 2008; Wichers et al., 2008) give strong support for circadian cortisol abnormalities such as increased cortisol awakening response (CAR), elevated evening levels or changes in overall diurnal variation.

In conclusion, data from previous studies give reasonable evidence for the existence of a hyperactive HPA axis in MS. However, methodological caveats arise from insufficient stratification in terms of disease course (e.g. active vs. stable), wide ranges in disease duration and heterogeneity in neurological disability. Accordingly, it is currently unclear whether HPA axis abnormalities are already present in early disease states or whether these abnormalities reflect a response to either acute inflammation or disease progression (e.g. loss of central feedback sites). Most studies explored HPA axis function in response to pharmacological stimulation (e.g. CRH test) or by one-point measurements in a potentially stressful hospital setting. Still little is known about basal circadian HPA axis function and CAR in MS patients. Furthermore, no study has so far addressed the influence of depressive symptoms on circadian HPA axis abnormalities.

In this study, we examined circadian HPA axis function and CAR in a homogenous sample of RRMS patients with maximum disease duration of 36 months.

In this context, our hypothesis states that circadian cortisol levels (including CAR and evening levels) do not generally differ between patients with early RRMS patients and healthy controls. We hypothesize that an elevated cortisol output (including greater CAR and elevated evening levels) is associated with depressive symptoms. We therefore assume that an elevated circadian cortisol response is observed in those MS patients who express elevated levels of depressive symptoms. In order to explore the influence of neurological impairment on circadian HPA axis function in early RRMS, a clinical disability score was also considered relevant.

2. Patients and methods

2.1. Patients and control subjects

Thirty-two RRMS patients (mean age: 30.53 years (19—43 years); 24 female/8 male) with clinically definite MS according to McDonald criteria (McDonald et al., 2001; Polman et al., 2005) were recruited in the local MS center. Mean disease duration was 14.34 months with a maximum time since diagnosis of 36 months (range: 2—36 months). All patients were clinically stable and had not received any glucocorticoid treatment four weeks prior to study entry. A total of 28 patients currently received immune modulating treatment. Sixteen age and sex matched healthy controls (HC) were recruited through local postings (mean age: 30.37 years (20—43 years); 13 female/3 male). For MS patients and healthy controls, exclusion criteria were: smoking (>5 cigarettes per day), a history of any psychiatric disorder, or pregnancy. MS patients were eligible if there was no corticosteroid treatment or relapse within the past 4 weeks. Written informed consent was obtained from each participant prior to study entry. The protocol was reviewed and approved by the local Ethics Committee (TU Dresden, Faculty of Medicine).

2.2. Cortisol assessment

Circadian cortisol release including CAR (Fries et al., 2009) was assessed on two separate days within a period of one