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Time matters – Acute stress response and glucocorticoid sensitivity in early multiple sclerosis

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ABSTRACT

Objective: Psychosocial stress has frequently been associated with disease activity and acute exacerbations in multiple sclerosis (MS). Despite this well established finding, strikingly little is known about the acute hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) stress response in MS.

Methods: Twenty-six early relapsing-remitting MS (RRMS) patients and seventeen age- and sex-matched control subjects (CS) took part in the Trier Social Stress Test (TSST), a well validated psycho-social laboratory stress protocol. Repeated blood samples were analyzed for stress-related cortisol and catecholamine levels as well as for glucocorticoid sensitivity (GCS) of target immune cells. Chronic and acute stress appraisals were assessed by self-report measures.

Results: RRMS patients and CS did not differ in stress-related cortisol/catecholamine levels, GCS or stress appraisal in response to the TSST. However, cortisol release as well as GCS was strongly correlated with time since diagnosis but not with neurological disability. Patients with shorter disease duration (2–12 months) expressed a significantly higher cortisol stress response while MS patients with longer disease duration (14–36 months) showed a significantly diminished HPA response as well as lower post-stress GCS.

Discussion: There is evidence for a time-dependent variability in the HPA stress system with an increased cortisol stress response in the first year after diagnosis along with a more blunted HPA stress response and a diminished GCS in subsequent disease stages. Data underscore the highly dynamic nature of HPA axis regulation in the MS disease process, which could possibly relate to compensatory mechanisms within a cytokine-HPA axis feedback circuit model.

1. Introduction

An increasing amount of research indicates that life stress potentially exerts profound negative effects on health and quality of life (Russ et al., 2012). In multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system, stressful experiences have repeatedly been associated with acute exacerbations and disease activity (Ackerman et al., 2002; Artemiadis et al., 2012; Buljevac et al., 2003; Mohr et al., 2004).

Acute or chronic life stress often causes marked changes in both sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) response systems. Activation of these systems is characterized by marked increases in systemic catecholamine and cortisol levels (Dickerson and Kemeny, 2004; Kirschbaum et al., 1993). Stress induced changes in cortisol and catecholamines also influence immune function at various levels (Elenkov et al., 2000; McEwen et al., 1997). In immune cells, glucocorticoids (GC) inhibit the inflammatory cascade (e.g. inhibition of pro-inflammatory cytokines) by interaction with cytoplasmatic transcriptional factors such as NFκB (McKay and Cidlowski, 1999). The degree of GC action depends on the glucocorticoid sensitivity (GCS) of cytoplasmatic glucocorticoid receptors, which is modulated by a variety of internal as well as external factors (e.g. stress) (Biddie et al., 2012; Rohleder

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et al., 2002). It therefore seems very likely that the impact of stress on acute exacerbations in MS is mediated by a fine tuned crosstalk between endocrine factors and the immune system (Kern and Ziemssen, 2008).

While there is reasonable support for the effects of life stress on MS exacerbations, so far, only two studies have assessed the acute stress response in MS patients. In one study, a robust SAM stress response was elicited (Heesen et al., 2002) but both stress protocols failed to induce a robust HPA axis activation (Ackerman et al., 1996; Heesen et al., 2002). Accordingly, endocrine stress response did not differ between patients and healthy control subjects (Ackerman et al., 1996; Heesen et al., 2002).

Several studies have shown that MS patients and healthy control subjects substantially differ in their GCS and changes in GCS have been associated with disease course, disease progression and treatment response to exogenous GC (e.g. methylprednisolone) (DeRijk et al., 2004; van Winsen et al., 2005, 2009, 2010). A recent study indicates that GCS undergoes dynamic changes in MS patients (Gold et al., 2012) but GCS in response to an acute stressor in MS patients has not yet been investigated.

To address these gaps in our current understanding of the role of stress exposure in MS, we set out here to study the acute SAM and HPA stress response along with measures of GCS in a homogenous group of RRMS patients at a relatively early disease state (maximum time since diagnosis $\leqslant$ 3 years). We administered a well validated psycho-social stress protocol that has proven to exert a reliable and robust autonomic as well as endocrine stress response (Dickerson and Kemeny, 2004; Kirschbaum et al., 1993). As previously shown, chronic stress (Rao et al., 2008), depressive symptoms (Rao et al., 2008), and cognitive appraisal (Gaab et al., 2005) act as potential modulating factors of the acute stress response. In order to control for these factors, we assessed levels of chronic stress, depressive symptoms and acute stress appraisals in all our participants.

2. Methods

2.1. Patients and control subjects

Twenty-six RRMS patients with clinically definite MS according to McDonald criteria (Polman et al., 2005) were recruited at the local MS centre. Mean disease duration was 16 months (median 13 months) with a maximum time since diagnosis of 36 months. All patients were clinically stable and had not received any steroid treatment four weeks prior to stress testing. Seventeen age-matched healthy control subjects (CS) were recruited through local postings. Characteristics for RRMS patients and CS are listed in Table 1. For MS patients and CS, exclusion criteria were: smoking (>5 cigarettes per day) or pregnancy. Further exclusion criteria for CS were: an existing autoimmune disorder or any known endocrine dysfunction. 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. Study procedure

The stress condition used in this experiment was the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993). The TSST consists of 3 min of preparation time, 5 min of free speech and 5 min of mental arithmetic in front of two panel members and a camera. The TSST reflects a well validated laboratory stress protocol that has repeatedly shown to induce robust activations of endocrine as well as autonomic stress response systems (Dickerson and Kemeny, 2004; Schommer et al., 2003). In order to control for circadian rhythms, all stress tests took place in the afternoon hours (2 pm–6 pm). Immune modulating treatment (RRMS only), oral contraceptives intake and menstrual cycle phase were assessed

Table 1
Characteristics and psychometric measures (depressive symptoms, acute and chronic stress) for MS patients and healthy control subjects. Raw scores are reported for all psychometric measures (SD = standard deviation).

	MS patients	Healthy control subjects
N	26	17
Age (range)	32.35 (19–43)	31.77 (22–44)
Gender (female/male)	17/9	12/5
EDSS (range)	1.81 (0–4.0)	–
Time since diagnosis in months (range)	16.04 (2–36)	–
Relapse within the last four months (yes/no)	6/20	–
Treatment		–
Interferon	14	
Glatirameracetat	6	
No medication	3	
Natalizumab	1	
Unknown	2	
Menstrual cycle/oral contraceptive		
Luteal	6	6
Follicular	2	4
None	0	1
oc	9	1
Depressive symptoms (BDI) (SD)	7.65 (5.85)	1.59 (1.54)
Chronic stress screening scale (TICS) (SD)	19.36 (6.35)	12.24 (6.91)
Perceived acute stress (PASA) (SD)	−1.42 (2.93)	−1.97 (2.31)
Relative maximum cortisol increase in response to the TSST (SD)	230.37 (135.85)	281.93 (212.76)

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