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Hypothalamo-pituitary-adrenal axis activity evolves differentially in untreated versus treated multiple sclerosis

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Summary
Background: Heterogeneous hypothalamo-pituitary-adrenal (HPA) system dysregulation has been shown in multiple sclerosis (MS), and cross-sectional studies suggested increasing hyperactivity with longer, progressing disease. Longitudinal studies to confirm this hypothesis and to study the impact of disease modifying treatment (DMT) have not been performed.
Objective/method: In order to determine the longitudinal evolution of HPA system activity in patients with MS, we performed an open follow-up evaluation of sixty patients with definite MS. Patients were untreated at baseline; at follow-up, 40 received DMT. From the combined dexamethasone/CRH test, performed at baseline and follow-up, we derived neuroendocrine indicators (maximum, maximum rise, mean location and area under the curve) for cortisol, ACTH and ACTH/cortisol ratio.
Results: In 20 patients who remained untreated (test—retest interval 28.8 ± 5.4 months), ACTH/cortisol ratios decreased significantly, driven by both mild increase in cortisol and reduction of ACTH secretion. In 40 patients with DMT (test—retest interval 15.5 ± 2.5 months), secretion of cortisol, ACTH and ACTH/cortisol ratios did not change significantly. There was significant, moderate correlation between baseline and follow-up tests for cortisol, but not for ACTH indicators. In untreated, but not in treated patients, change in ACTH/cortisol ratios showed moderate inverse correlation to the time interval between tests (Pearson: beta −0.52 to −0.56, $p < 0.05$); the relation to progression of neurological disability was not significant.

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Conclusions: HPA axis activation in untreated MS drifts from hypothalamo-pituitary to more adrenal activation, consistent with adrenal sensitization or hypertrophy due to chronic HPA axis activation. HPA system regulation remains more stable in MS patients on DMT.

1. Introduction

Multiple sclerosis (MS) is the most common central nervous system (CNS) demyelinating disease of adulthood, and is responsible for a substantial burden of impairment (Compston et al., 2005). Although the cause of the disorder remains unknown (and is probably multifactorial), an autoimmune process is widely accepted as central in the pathogenesis. In addition to primarily intrinsic regulation, the various components of the immune response which are implicated in the pathogenesis of MS are also controlled extrinsically by the endocrine system (Webster et al., 2002). Among the endocrine effectors, the immunosuppressive action of glucocorticoids, whose secretion from the adrenals is delicately regulated within the hypothalamo-pituitary-adrenal (HPA) axis, is best established. Supported by therapeutic efficacy of glucocorticoids in MS relapses, HPA axis activity has therefore been studied in order to gain additional insight into the pathogenesis and neuroendocrine–immune interactions. Overall, the recent literature consistently shows an activation of the HPA axis under basal conditions (Michelson et al., 1994), in dynamic testing (Reder et al., 1987; Michelson et al., 1994; Wei and Lightman, 1997; Fassbender et al., 1998; Ysrraelit et al., 2008) or at post-mortem (Reder et al., 1994; Erkut et al., 1995; Purba et al., 1995). Neuropathologically, the assumed direct stimulation of CRH secreting neurons by inflammatory plaques could not be confirmed (Huitinga et al., 2004).

Using the combined dexamethasone–corticotropin releasing hormone test (Dex–CRH test), we and others have previously shown hyperactivity of the HPA system in MS patients, which was significantly correlated to the clinical course of MS, with relapsing-remitting MS showing the mildest, and primary-progressive MS the most pronounced changes compared to healthy controls (Grasser et al., 1996; Then Bergh et al., 1999; Heesen et al., 2002). The chronic hypersecretion of cortisol implied by these findings leads to a desensitization of immune cells towards the effects of endogenous corticosteroids and could thus have an impact on the course of the disease.

In order to estimate the pathophysiological significance of this hypercortisolism, cross-sectional analyses have been performed and demonstrated more pronounced hypersecretion of ACTH and cortisol with more severe neurological disability (Then Bergh et al., 1999), secondary and especially primary progression (Then Bergh et al., 1999; Heesen et al., 2002), cognitive disturbance (Heesen et al., 2002) and fatigue (Gottschalk et al., 2005), as well as brain atrophy as measured by third ventricle volume (Schumann et al., 2002). While these data do suggest a link between the degree of dysregulation and disease progression, information on longitudinal evolution of HPA activity and correlation with disease progression would help support that hypothesis. In addition to observing the spontaneous course, the impact of disease modifying therapies (DMT) on immediate hormone secretion and HPA-axis dysregulation has only been studied in a small cohort over a three-month period (Kümpfel et al., 2000; Then Bergh et al., 2007). We therefore studied if HPA regulation changes over an extended period of time, whether it correlates to clinical disease progression and whether it is influenced by DMT.

2. Subjects and methods

2.1. Study design

We included patients with clinically definite multiple sclerosis according to Poser criteria (Poser et al., 1983) for repeat neuroendocrine testing. Patients with endocrine, other chronic autoimmune disorders, or psychiatric diseases (unipolar depression or mania, bipolar affective disorder, schizophrenia, personality, dissociative and psychosomatic disorders) were excluded, as were those receiving antidepressants or endocrinologically active medication (with the exception of L-thyroxine for endemic (presumed iodine-deficiency) hypothyroidism). At least one month had to have passed since any application of systemic glucocorticoids (e.g., for MS relapse). Patients were naïve to (immunomodulatory or immunosuppressive) DMT when undergoing the baseline evaluation; DMT was recommended where clinically indicated according to current recommendations. Re-testing of patients receiving DMT was not performed until flu-like side-effects had subsided in order to exclude confounding effects.

Neuroendocrine testing was performed on an outpatient basis. Patients were examined clinically to rule out acute illness and MS relapse, and neurological impairment was rated using the expanded disability status scale (EDSS) (Kurtzke, 1983). The EDSS is a quantitative measure of disability, combining objective findings on neurological examination and walking range; it is a non-linear scale ranging from 0 (no disability) to 10 (death due to MS), in 0.5 point increments. EDSS was performed as part of the clinical routine at baseline. At follow-up, the neurologist rating disability was kept unaware of the patient's current treatment, although we cannot exclude that he had previously seen the patient in clinic, potentially compromising blinding. A comprehensive psychiatric interview was performed to exclude patients with clinically relevant depression. Complete blood count, serum chemistry, CRP, TSH and free thyroid hormones, and a urinalysis was performed. Patients with normal results underwent the combined dexamethasone/CRH test two days later.

2.2. Subjects

Sixty patients who had undergone the combined dexamethasone/CRH test at least 12 months before agreed to retesting.