Low Adrenal Cortisol Levels In MS Lead To A Worse Disease Outcome

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During multiple sclerosis (MS), an inflammatory demyelinating disease of the central nervous system (CNS), activation of the hypothalamo-pituitary-adrenal (HPA) axis is considered to modulate the immune system in such a way that the probability of recovery from a relapse is increased. In a series of postmortem studies we observed a significant activation of corticotropin releasing hormone (CRH) neurons and increased cortisol in the cerebrospinal fluid (CSF) of MS patients, indicating activation of the HPA axis in this disease. On the other hand, sepsis, while elevating cortisol in control subjects, did not associate with a further increase of cortisol in MS patients. Thus, the activated HPA-system in MS does not respond to an acute inflammatory stimulus. In order to investigate the role of chronic inflammation in the CNS in the activation of the HPA axis in MS, MS lesions in the hypothalamus were quantified and interleukin (IL)-6 levels in the CSF were determined. There was no difference in IL-6 levels between MS and control patients. A positive correlation was found between cortisol and IL-6 in control subjects with sepsis, but not in MS patients with sepsis or MS and control groups without sepsis. Thus, IL-6 in the CSF of MS patients is not the cause of the activation of the HPA system in MS. We found a remarkably high incidence (95% of the patients) of MS lesions in the hypothalamus, of which the majority (60%) were active. The more active lesions were present in the hypothalamus, the shorter the disease duration to the moment of death, indicative of a worse disease course. Preliminary data show suppression of the activation of CRH neurons by active hypothalamic MS lesions. We propose that this suppression of CRH neurons by active hypothalamic MS lesions causes the concomitant unfavorable disease course via an inadequate cortisol response during relapses of MS.