

Interrelation between MR based surrogate markers of multiple sclerosis, disease severity and altered neuroendocrinological functioning

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Synopsis

Hyperdrive of the hypothalamo-pituitary-adrenal (HPA) axis is associated with a chronic course of multiple sclerosis (1) and enlarged ventricles (2). To further investigate the potentially disease modulating role of neuroendocrinological malfunctioning, 26 MS patients were characterized for HPA functioning, EDSS, proton spectroscopy of the hippocampal region and parietal white matter, T2 lesion load (LL) and the brain parenchymal fraction (PBF). Spearman's rank correlation tests revealed a significant negative association between EDSS and hippocampal NAA/Cr ($\rho = -0.647$) and PBF (-0.475). NAA/Cr was negatively associated with T2LL ($r = -0.508$ white matter, -0.587 hippocampus), but not with PBF. No correlations emerged with HPA hyperdrive.

Introduction

Multiple sclerosis was found to be associated with altered functioning of the hypothalamo-pituitary-adrenal (HPA) axis, namely a hyperdrive mainly in chronic disease stages (1) and in some individuals a hypodrive. This neuroendocrinologic malfunctioning is thought to be the consequence of the chronic inflammatory process, but the underlying mechanisms are poorly understood. In line with this hypothesis we identified a negative correlation between MR markers of inflammatory disease activity, i.e. the number of Gd-enhancing lesions and HPA drive (2). Moreover, we demonstrated a positive association between ventricular volume and the cortisol response to DEX-CRH, a valid marker of HPA hyperdrive (2). The nature of this interrelation remained obscure and was further investigated in this combined MRS, MRI and neuroendocrinological study. The hippocampus was targeted as prime region of interest because (i) it contributes to regulating HPA axis function, such that disease-related neuronal/axonal impairment may lead to HPA hyperdrive and conversely (ii) elevated glucocorticoids may impair hippocampal neurons. We thus studied hippocampal MRS and the combined dexamethasone suppression, CRH stimulation (DEX-CRH) test in a prospective sample of MS patients together with other MR markers of global disease burden such as T2 lesion load, global brain atrophy and white matter NAA/Cr.

Material and Methods

26 MS patients (19 relapsing-remitting, 4 secondary progressive and 3 primary progressive, 18 women, 8 men, mean [SD] age 38.4 [9.8] years) were enrolled after giving informed written consent. EDSS ranged from 1 to 6.5 (mean 2.7) and mean duration of disease was 7.1 years (SD:5.8). The standardized DEX-CRH test was performed as previously described (1,2). The overall CRH induced cortisol response was expressed as $\ln(\text{area under the curve, AUC})$ assuming a trapezoidal shape with one baseline and 6 post CRH measuring time points over 90 min.

MRS and MRI were acquired on a clinical scanner (1.5T, GE Medical Systems, MI). A PRESS sequence (probe-p, TR=2000/TE=70ms, 128 averages) was used for hippocampal ¹H MRS from a rectangular box (30x12x17 mm, n=25). For white matter spectra (n=26), a STEAM sequence was used (TR/TE=3000/30ms, 128 averages), the voxel was positioned in parietal white matter aiming to best exclude visible plaques. Spectra quantification was done using the LCModel (3) deploying basis datasets with simulated lipids (4). Only relative concentrations of NAA/Cr were tested thus excluding atrophy or partial CSF volume confounds.

MRI comprised coregistered 24 slices (4mm, 1 mm gap) parallel to the AC-PC line (PD-, T2-, T1-, MT-T1-, Gd-enhanced T1- and MT-T1 – as well as FLAIR weighted). After manual brain extraction and correcting global signal intensity inhomogeneities, these multimodal images were segmented using a supervised clustering algorithm allowing to determine T2 weighted lesion load (T2LL) and the brain parenchyma fraction (PBF) in 20 patients.

Correlation analysis was done deploying Spearman's rank correlation coefficients and Pearson's correlation coefficients as appropriate.

Results

Mean T2LL was 18.9 ml (SD: 16.8) and mean PBF was 0.853 (SD:0.044). Correlation analysis of MR markers and EDSS revealed the closest correlation between disease severity and hippocampal NAA/Cr ($\rho = -0.647$, $p < 0.001$, $n = 25$), followed by PBF ($\rho = -0.475$, $p = 0.034$) and only a trend effect for T2LL ($\rho = 0.401$, $p < 0.1$). Age was negatively correlated with PBF ($r = -0.530$, $p = 0.016$) only. T2LL correlated negatively with NAA/Cr in white matter ($r = -0.508$, $p = 0.022$) and the hippocampal region ($r = -0.587$, $p = 0.005$). PBF did not correlate with NAA/Cr or T2LL. There was a trend towards negative correlation between hippocampal NAA/Cr and $\ln\text{AUC}$ probably being due to one subject. No correlation was found between $\ln\text{AUC}$ and EDSS, age, T2LL or PBF.

Conclusion

In this sample of MS patients, alterations of the HPA axis were dissociated from MR surrogate markers of disease burden (T2LL), global markers of neurodegeneration (brain parenchyma fraction) and spectroscopic markers of neuronal integrity. As regards the potential interrelation between hippocampal NAA/Cr and HPA hyperdrive, the trend effect and small sample size caution against a type II error. Moreover, reduced hippocampal NAA/Cr with predominant grey matter contribution was found to be closely related with disease severity (explaining >40% of the mutual variance) and moderately with T2LL. This suggests a disease-conditioned neuronal impairment which warrants further investigation in view of the unresolved neural basis of cognitive dysfunction in MS (5).

References

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