Cerebral Metabolic Changes in Rheumatoid Arthritis

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Purpose: Rheumatoid arthritis (RA) is a systemic inflammatory disease predominantly characterized by synovial inflammation. The incidence of extra-articular involvement is about 1 per 100 person-years and is associated with increased morbidity and mortality. (1) Neurological symptoms are scarce in RA patients, polyneuropathy secondary to vasculitis being the most frequent. There are only a number of case-reports reporting cerebral vasculitis in RA. (2) A more well known feature of RA is fatigue with an estimated 80% to 93% of individuals with RA experiencing fatigue (3), and 57% identify fatigue as the most problematic aspect of their condition. (4) Fatigue is an integral feature of the disease and the American College of Rheumatology (ACR) identifies its absence as a criterion for remission. (3) The effects of RA on brain metabolism are currently unknown. The aim of the present study was to detect possible cerebral metabolic abnormalities in RA patients using proton magnetic resonance spectroscopy (1H-MRS).

Methods: 35 RA patients (6 male; 29 female; age average: 51.8 years; standard deviation 14.6) with varying disease activity and 28 healthy age and sex-matched control subjects were subjected to single voxel 1H-MRS using a double spin-echo PRESS sequence. The dimensions of the selected volumes-of-interest were typically 40 mm in anterior-posterior, 15 mm in left-right directions and 10 mm in caudo-cranial directions. Special care was taken to exclude gray matter and CSF. Measurement parameters were: TR: 2000 ms, TE: 136 ms, 2048 time domain data points, 2000Hz spectral width and 128 signals acquired. After zero-filling to 4096 data points, exponential multiplication of 2 Hz, Fourier transformation and linear baseline correction, N-acetylaspartate (NAA) (referenced at 2.0 ppm), choline and total creatine peaks were quantitated using integration software routines, which were provided by the manufacturer. Patients with a history of neurological signs or symptoms were excluded from further analysis. The volume-of-interest (VOI) was selected in the left centrum semi-ovale. The following ratios were calculated: n-acetylaspartate (NAA)/choline, NAA/creatine and choline/creatine.

Results: The comparison of the group of control subjects with the group of RA patients did not show any significant difference in metabolite ratios. However, in active RA patients (erythrocyte sedimentation rate (ESR)>25) NAA/choline ratios were decreased (p<0.05) and choline/creatine ratios were increased (p<0.05) compared to inactive (ESR<25) RA patients. Moreover, these ratios correlated significantly (r=-0.37, p<0.05 and r=0.45, p<0.05 respectively) with the ESR. Patients treated with methotrexate demonstrated higher NAA/choline ratios (p<0.05) and lower choline/creatine ratios (p<0.05) compared with patients not treated with methotrexate. A backward linear regression analysis, with the NAA/choline and choline/creatine ratios as dependent variables and the ESR and MTX as independent variables, excluded MTX as a predictor in the correlation between the ESR and the NAA/choline or the choline/creatine ratio.

Conclusion: Our data show that MR spectra in RA patients with active disease are characterized by an increased choline concentration, suggesting impaired membrane related metabolism. Although we did not find significant differences in brain metabolites between control subjects and RA patients as a whole, cerebral choline levels in RA patients are dependent on the systemic disease activity of RA, resulting in both increased and decreased choline concentrations. In future studies the issue needs to be addressed whether these metabolic alterations are associated with non-specific neurological symptoms, such as fatigue and lack of concentration.