Cognitive impairment in early multiple sclerosis related to metabolic impairment in cerebellum

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Background: While metabolic changes and cognitive impairment are known to be present in multiple sclerosis (MS) from the earliest stage of the disease, no exhaustive examinations have been performed to assess potential relationships between metabolite levels and cognitive status.

Objective: This study aimed to investigate whether magnetic resonance spectroscopic markers in normal appearing brain tissues are related to cognitive status in multiple sclerosis.

Methods: A five-year ^{1}H magnetic resonance spectroscopic imaging follow-up (baseline – year3 – year5) was performed on 23 patients with clinically isolated syndromes suggestive of MS (20 women, 3 men - mean age 32 yo) and 24 matched controls. MR experiments were performed on a 1.5T Vision system (Siemens, Erlangen, Germany) using a transmit-receive head coil. A single slice multivoxel ^{1}H MR spectroscopy was performed in the sagittal plane using a home-designed acquisition-weighted, hamming shape, 2D-SE pulse sequence with the following parameters: TE = 135 ms, TR = 1500 ms, slice thickness = 15 mm, FOV = 240x240, 21x21 pseudo-circular encoding steps, resulting in a nominal spatial resolution of 11 mm and leading to 524 free induction decays acquired in 12 minutes. The spatial resolution was defined as the width of the spatial response function at 64% of maximum [1] resulting in an effective resolution of 22 mm and a voxel volume of 5.7 mL. Due to the pseudocircular spatial k sampling, voxel shape was cylindrical (Fig 1). All radio-frequency pulses were optimized and generated using the Matpulse software [2]. The water/lipid suppression scheme was implemented according to Tkac et al. [3] with outer volume saturation and chemical selective saturation schemes to suppress scalp fat and water signals. Relative concentrations of N-acetylaspartate (NAA), creatine compounds (Cr) and choline-containing compounds (Cho) were assessed on normal appearing brain tissues (splenium of corpus callosum, posterior cingulum and cerebellum) (Fig 1). For relative quantification, the value of each metabolite was divided by the sum of NAA, Cr and Cho signals from the same spectrum [4]. For each subject, cognitive status was assessed by an extensive neuropsychological test battery at year 5 using the Brief Repeatable Battery [5]. A cognitive impairment index was used to provide a composite measure of cognitive dysfunction. Putative correlations between spectroscopic and cognitive data were assessed by performing both parametric and non-parametric statistics using JMP.

Results: At 5 years, 10 patients presented impaired cognitive functions and 13 patients were unimpaired. NAA level in cerebellum was significantly lower (p=0.01) and choline level in splenium was significantly higher (p<0.01) in impaired cognitive patients compared to unimpaired cognitive patients and controls at 5 years. Among all metabolites, only NAA levels in cerebellum showed a different evolution over time between impaired and unimpaired cognitive patients with a clear dissociation between the two groups that occurred after 3 years (Fig 2).

Discussion and Conclusion: In MS patients, metabolic impairment occurs even in normal appearing tissues since the earliest stage of the disease. It appears that cerebellum neuronal dysfunctions are more involved in cognitive impairment in multiple sclerosis compared to white matter (splenium) or grey matter (posterior cingulum) regions.

Fig 1: Location of voxels
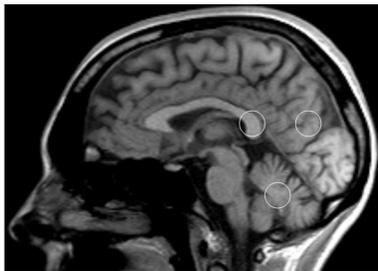
Fig 2: Evolution of NAA level in cerebellum
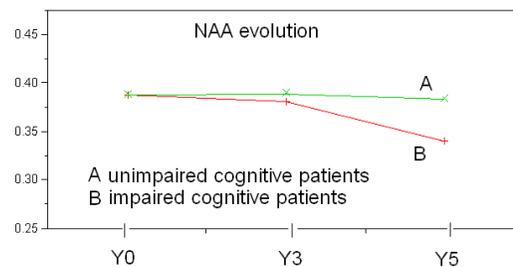
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