Relation between axonal damage and inflammation by 1H-MRSI and T2-weighted lesion volume in early relapsing remitting Multiple Sclerosis. The effect of subcutaneously Interferon beta-1a

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Introduction:
Multiple sclerosis (MS) is an inflammatory demyelinating disease with long prominent neural tissue degeneration of unknown origin. Recently, Magnetic Resonance Imaging (MRI) and pathological studies have reported the importance of neuronal and axonal damage in the early stages of the disease. There is a general agreement that disability is related to the cumulative axonal damage that happens throughout the patients' lifetime, but its role in earliest stages of the disease is still under evaluation. The mechanisms of axonal dysfunction, loss, and "ongoing axonal damage" in normal appearing white matter and grey matter remain poorly understood. The objectives of this study are first, to examine the relationship between axonal damage in the normal appearing white matter of brainstem and inflammatory activity in patients with an early relapsing remitting multiple sclerosis. The second objective is to assess the effects of interferon beta-1a (IFNB1a) on metabolic brainstem changes and parameters of inflammation.

Methods:
With this purpose we studied sixteen multiple sclerosis patients treated with IFNB1a, twenty multiple sclerosis patients untreated and ten age-matched healthy subjects prospectively for two years. Relapse rate was calculated annually. T2-weighted MRI and in vivo 1H-MRS imaging at echo time 272 ms were acquired at recruitment and annually. The brain T2-weighted lesion volume was calculated with a semiautomatic program. N-Acetylaspartate (NAA), Creatine (Cr) and Choline (Cho) resonances areas were integrated with jMRUI program and the ratios calculated for the sum of the volume elements that represented the brainstem. Disability was rated with the expanded disability status scale (EDSS) and the multiple sclerosis functional composite scale.

Results:
The basal NAA/Cho ratio at brainstem was significantly decreased in multiple sclerosis patients compared with controls. After two years, there was a decrease in the NAA/Cho (-9%) and the NAA/Cr ratio (-15%) while the T2-weighted lesion volume increased (18%) in multiple sclerosis patients. Control group did not express any significant change. A subgroup analysis showed a higher NAA/Cho decrement in multiple sclerosis patients with more than one relapse at follow-up. Brain NAA/Cho correlated with EDSS. At the end of the study a inverse correlation was found between NAA/Cho ratio and T2 lesional volume (p=0.008). IFNB1a was effective in reducing disease activity (annual relapse rate and T2-weighted lesion volume) but appears ineffective in delaying neuroaxonal loss (treated and untreated multiple sclerosis patients suffered similar metabolic decrements).

Conclusions:
This work suggests that axonal damage begins and progresses from early stages of the multiple sclerosis. In the earliest stages of multiple sclerosis, clinical and radiological evidence of inflammation is partly related to progressive axonal damage, and however the stabilizing effect of IFNB1a on inflammatory activity appears not to be sufficient to reduce neuroaxonal damage in a short-term study. Analysis with longer periods of observations are need to confirm or no these preliminary findings.

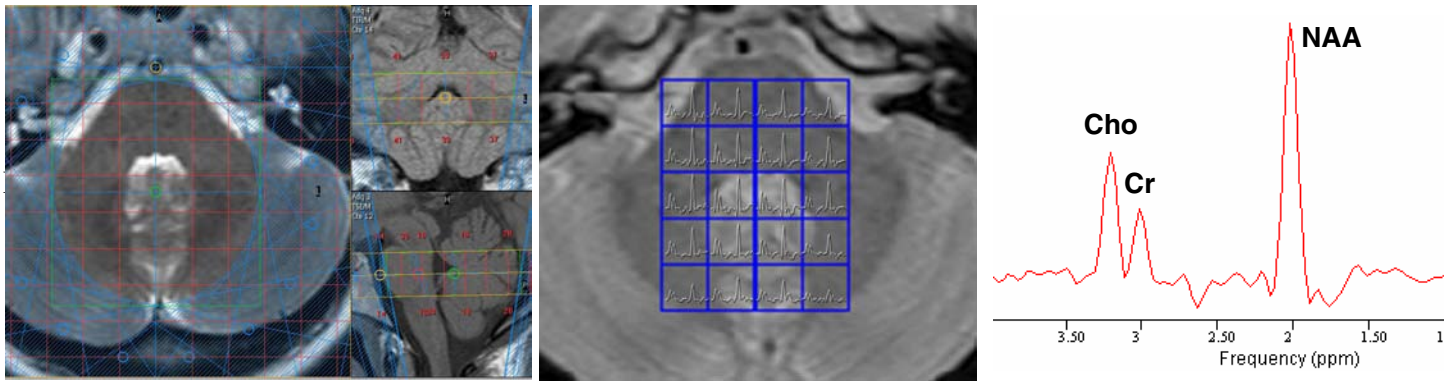

Figure 1:
Left: Axial, sagittal and coronal view of the multivoxel location on brainstem. Centre: location and matrix of spectra aquired on brainstem and cerebellum showing those spectra in the regions of interest. Spectra on brainstem were chosen to be added into a representative spectrum, four spectra inside the black dotted line. Right:: Spectra representing the brainstem at long echo time with the main resonances, NAA, Creatine and Choline.

This work was partially funded by National Grants from the Science and Education Ministery (SAF2004-06297 and SAF2004-20971-E) and Health Ministery (ISCIII2003-G03/185) of the Spanish Government and by Laboratories Serono.