Staging of Progressive Multifocal Leukoencephalopathy Lesions using Proton MR spectroscopy at 3 T

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Abstract: PML is a deadly demyelinating disease of the brain affecting HIV-infected individuals with AIDS. The purpose of this study was to investigate metabolic changes which may serve as markers for the detection and staging of PML lesions (in a background of HIV encephalopathy). LCModel, an automated fitting approach, was utilized in the analysis of both single voxel and CSI proton spectra of the lesions. PML lesions were distinguished from HIV encephalopathy by a higher Cho/Cr concentration ratio and elevated lipid signals. Sub-acute and chronic lesions were differentiated by the level of Cr/Cho+Cr/NAA, which was significantly lower in the sub-acute lesions.

Introduction: Progressive multifocal leukoencephalopathy (PML) is a deadly demyelinating disease of the central nervous system caused by the polyomavirus JC (JCV), for which there is no specific treatment. PML affects HIV-infected individuals with CD4 counts < 200/μl (AIDS). This disease is characterized by progressive neurological deficits including motor and sensory dysfunction as well as dementia leading usually to death, with an average survival of only ten months despite highly active antiretroviral therapy (HAART). Unlike other opportunistic infections, PML continues to occur in patients who respond to antiretroviral treatment as measured by suppression of HIV viral replication.

PML lesions show hyperintense signals on T_2-weighted MR images in the affected white matter. However, distinction between active and chronic lesions of PML is impossible using MRI [1]. In addition lesions of PML can be difficult to distinguish in a background of HIV encephalopathy as the latter shows similar hyperintense signal in T_2-weighted images without mass effect and contrast enhancement. Nevertheless, magnetization transfer MR imaging has been previously shown to improve the differentiation between PML and HIV-white matter lesions in patients with AIDS. MR spectroscopy has been previously utilized as a non-invasive tool to study the effects of HIV on brain metabolism and the metabolic alterations that are associated with PML [2-5].

Design and Methods: The target population of this study was HIV-infected patients with biopsy proven PML or with CSF JCV PCR +. We have examined 9 HIV+ patients with 17 PML lesions including 9 sub-acute and 8 chronic lesions. Four of the sub-acute and one of the chronic lesions were followed longitudinally (2 or 3 times in up to 9 months). The location of these lesions was determined using T_2-weighted MR imaging. The metabolic characteristics of the affected brain region were evaluated by proton MR spectroscopy at 3 T (GE medical systems, Waukesha, WI) employing PRESS (TE 35 msec, single voxel at the lesion and 2D-CSI at the same slice) and analyzed by LCModel [6-7]. The results are presented in terms of averaged concentration ratio ± SD of choline metabolites (Cho), N-acetylaspartate and N-acetylaspartate-glutamate (NAA), and myo-Inositol (mI) with reference to creatine metabolites (Cr).

Results: LCModel was successfully applied in the analysis of PML lesions (Fig.1). The PML lesions studied here (23 examinations) showed high Cho/Cr, low NAA/Cr, and high mI/Cr (0.36 ± 0.09, 1.19 ± 0.47, and 0.96 ± 0.40, respectively) compared to the normal concentration ratios found in white matter [8]. Sub-acute lesions were significantly differentiated from chronic lesions due to their higher levels of Cho/Cr and NAA/Cr, expressed as a lower value of Cr/Cho + Cr/NAA in the sub-acute lesions, p=0.020 two-tail t-test, (Fig. 2). The increase in mI appeared uniformly distributed among the lesions. Elevated resonances at ~0.9 and ~1.3 ppm (lipids or macromolecules) were usually observed.

Four of the five lesions followed longitudinally have shown an about 2 fold increase in their Cr/Cho + Cr/NAA during 3 to 9 months, in agreement with the shift into a chronic stage. The fifth lesion showed a slight (~25 %) decrease in this metabolite ratio.

Discussion: The metabolic "finger print" of PML appears different than that of HIV encephalopathy progression. The latter is associated with elevated myo-inositol levels with all other metabolites at their normal levels followed by a marked decrease in NAA level. PML is characterized by all of the above with an increase in Cho/Cr as well as increased lipid or macromolecule signals, differentiating it from HIV encephalopathy. These metabolic changes in PML are consistent with demyelination, disruption of axonal function, and neuronal loss.

In addition to differentiating PML lesions from HIV encephalopathy, MR spectroscopy enabled the discrimination between active and chronic PML lesions. This is extremely valuable since there are currently no biological markers for the evolution of PML.

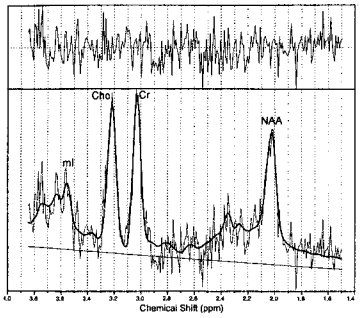

Fig. 1. Lower panel: a proton MR spectrum of a chronic PML lesion at the cerebellum. The thick line is the LCModel fitting result of the original spectrum (thin line). The residual noise is shown on the top panel.

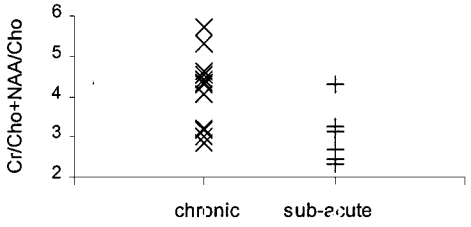

Fig. 2. The level of Cr/Cho+Cr/NAA in chronic (x) and sub-acute (+) PML lesions.

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