Reduced fat fraction in calvarial marrow of HIV-infected patients

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Introduction

Reduced fat content in bone marrow is recognized as an early marker of systemic disease in adults. Although marrow is predominantly hematopoietic at birth, it becomes largely inactive (or 'fatty') by early adulthood in healthy individuals. Fatty marrow may however reconvert to cellular marrow in response to systemic disease, due either to pathologic replacement, or to increased demand for hematopoiesis [1]. In HIV, changes in bone marrow can occur both from complications of the disease, such as anemia [2], and from side effects of antiretroviral drugs, such as lipodystrophy [3,4]. MRI provides a noninvasive means to measure the fat content of bone marrow, and can be applied in regions inaccessible to biopsy or aspiration. In this study, calvarial bone marrow was imaged using a modified Dixon technique, as part of a comprehensive neuroradiological assessment. The measured fat fraction showed a significant reduction in HIV-infected patients as compared to control subjects.

Methods

Subject Cohort

Patients were drawn from the Northeast AIDS Dementia Cohort Study [5], a longitudinal investigation of the natural history of neurologic impairment in HIV infection. MRI scans were performed in ten patients, all of whom were in advanced stages of HIV infection as determined by serology and CD4 counts. They all met the criteria for AIDS on the basis of a history of AIDS-defining illnesses, and were receiving highly active antiretroviral therapy (HAART). They had a mean age of 50.4 years (std 7.7, range 38 – 63), and included 2 blacks, 1 Asian and 7 whites, 2 women and 8 men. Ten control subjects were chosen to match the patients approximately in terms of age, ethnicity and gender. They had a mean age of 44.0 years (std 10.1, range 23 – 57) and included 2 blacks and 8 whites, 2 women and 8 men.

Image acquisition

Imaging was performed on a GE Healthcare 1.5T Signa 11.0 Twinspeed system with a quadrature birdcage head coil, using a multipoint modified Dixon technique. A single mid-sagittal slice was prescribed in the head, and 17 images were acquired using a fast gradient-echo sequence with TE values of 1.8 – 6.6 ms in increments of 0.3 ms. The remaining parameters, which were held constant over all acquisitions, were TR = 20ms, FA = 15°, FOV = 24cm, slice thickness = 8mm, BW = ±125kHz, matrix size = 256x256, NEX = 4. In addition to the magnitude image, the real and imaginary parts of the complex image were saved for their phase information.

Image analysis

In each subject, several regions of interest (ROIs) were drawn in the calvarial marrow on the in-phase image (TE = 4.5 ms). The ROIs were distributed mainly over the frontal and occipital bones, and numbered between 3 and 9, depending on the location and extent of the marrow. Each ROI was then transposed onto the other images, making slight adjustments in position where necessary to account for head displacement. The complex signal amplitude was averaged over the ROI for each TE value, and its magnitude was evaluated as a measure of mean signal intensity. The intensities of the fat and water components I_f and I_w were determined by adding or subtracting the in-phase (TE = 4.5 ms) and out-of-phase (TE = 2.4 ms) signal intensities as appropriate, making adjustments for T_2* relaxation. The T_2* values for water and fat were estimated using the signal amplitude of the second out-of-phase image (TE = 6.6 ms). The remaining data points were not used directly in the calculations, but provided a check that the frequency offset due to B_0 inhomogeneity was less than the chemical shift. The fat fraction was calculated from $F = I_f / (I_f + I_w)$.

Statistical analysis

A representative fat fraction was obtained for each subject by averaging the values calculated for each ROI. The fat fraction was then compared in HIV-infected and control groups using an analysis of variance (ANOVA) model, with age included as a covariate. Statistical analyses were performed using SPSS (Chicago, IL).

Results

An in-phase image from a control subject is shown in Fig 1. The complex signal data from an ROI in the calvarial marrow of this subject are displayed in Fig 2a. Note that the data encircle the origin with increasing TE, indicating that the signal is fat-dominated. The equivalent data from an HIV-infected patient are shown in Fig 2b. The fact that the patient's data do not encircle the origin indicates that the signal from his marrow is water-dominated. The fat fractions in all subjects were calculated using estimated T_2* values for fat and water of 9ms and 14ms respectively. For the control subjects the fat fraction was found to be 0.71 ± 0.17 (mean ± std), whereas for the HIV-infected patients it was 0.56 ± 0.23. The difference between the groups is significant, controlling for the effects of age ($F(1,17) = 6.198$; $p = 0.023$).

Discussion

The fat fraction in calvarial marrow was found to be significantly reduced in HIV-infected patients, and may provide useful information regarding the progression of disease, and the effects of antiretroviral therapy on lipogenesis and lipolysis. In this subject cohort however it was difficult to distinguish drug-related from disease-related factors, since the patients had taken many of the same drugs during the course of their treatment. Note that since the MRI fat fraction is defined in terms of a ratio of signal intensities, its value cannot be directly equated to fat content as measured by biopsy, or compared across different MRI protocols.

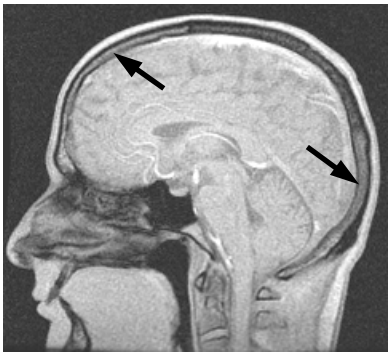

Fig. 1: In-phase image (TE = 4.5ms) from a control subject. Arrows indicate marrow in the frontal and occipital bones.

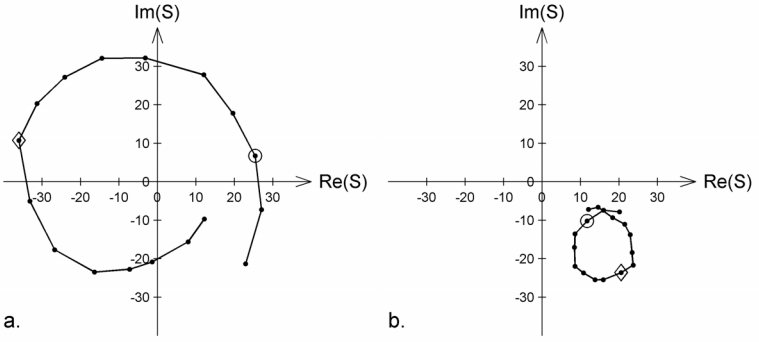

Fig. 2: Average signal from an ROI in the calvarial marrow of a control subject (a) and an HIV-infected subject (b). The signal data are plotted in the complex plane for TE values ranging from 1.8ms to 6.6ms. The circled point corresponds to the out-of-phase value (TE = 2.4ms), while the diamond encloses the in-phase value (TE = 4.5ms).

References: [1] Loevner LA *et al.* AJNR 2002; 23: 248-254, [2] Moyle G AIDS Rev 2002; 4: 13-20, [3] Mulkern RV *et al.* MRM 2004; 52: 552-558, [4] Jain RG *et al.* J Biol Chem 2002; 277: 19247-19250, [5] Marder K *et al.* Neurology, 1996; 47:1247-1253

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