Whole Brain Magnetization Transfer Histogram Analysis of Pediatric Acute Lymphoblastic Leukemia Patients Receiving Intrathecal Methotrexate Therapy

A. Yamamoto[1], Y. Miki[1], K. Togashi[1], M. Kanagaki[1], Y. Fushimi[1], T. Okada[1], S. Adachi[2], M. Kobayashi[2], T. Nakahata[2]

[1]Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University, Kyoto, Kyoto, Japan, [2]Department of Pediatrics, Kyoto University, Kyoto, Kyoto, Japan

INTRODUCTION

Current treatment of children with advanced acute lymphoblastic leukemia (ALL) has dramatically improved the outcome. Under employment of the prophylactic CNS-directed intensive chemotherapy, such as intrathecal methotrexate (MTX) injection, subsequent chemotherapy-related encephalopathy has become a concern. Chemotherapy-related encephalopathy may show regions of hyperintensity in white matter on T2-weighted magnetic resonance (MR) images. Magnetization transfer (MT) imaging and magnetization transfer ratio (MTR) histogram analysis of the whole brain are techniques that are sensitive to the presence of myelin in the brain and that has been proved to be a very feasible method to evaluate microscopic parenchymal changes which are normally appearing on conventional MRI sequences [1-4]. The purpose of this study is to evaluate the feasibility of whole brain MTR histogram analysis in children receiving chemotherapy for ALL.

METHODS

This prospective study consists of consecutive 10 pediatric ALL patients (3 female and 7 male, 0 - 16 years-old, mean 6 years-old). MR examinations of the brain were performed before and after chemotherapy for these 10 patients on a Signa Horizon (General Electric Medical Systems, Milwaukee, Wis) 1.5-T unit equipped with a quadrature transmit/receive head coil. Pre-chemotherapy scans were performed within 1 day before start of chemotherapy for ALL. Post-chemotherapy scans were performed 0 to 5 (mean 1.8) weeks after the last intrathecal injection of MTX. MR imaging consisted of routine conventional sequences and MT sequences. Routine conventional sequences are T1-weighted axial images, fast spin-echo T2-weighted axial images, and axial fluid attenuated inversion recovery (FLAIR) images. All routine sequences are 3 mm slice thickness, 1 mm slice interval and 22 cm field of view (FOV). Routine conventional MR images were evaluated by neuroradiologists for presence of abnormal signals in white matter. MT imaging was performed with a three-dimensional gradient-echo pulse sequence with parameters of 106 ms / 5 ms / 1 (TR/TE/NEX) and a 12° flip angle. A matrix of 256 × 256 was used for a total of 24 sections with a section thickness of 5 mm. The field of view was 22 cm. Two consecutive sets of axial images were obtained: the first set with the radio-frequency (RF) saturation pulse on and the second with the saturation pulse off. A sinc-shaped RF saturation pulse with an average field intensity equal to 3.67×10^{-6} T was applied at a frequency 2 kHz below water resonance [5]. Image postprocessing was performed on a homemade PC-LINUX workstation using 3DVIEWNIX software (Medical Image Processing Group, Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA). Image postprocessing consisted of the following steps. The first step consisted of segmenting the brain from its surroundings. This was obtained by a semiautomated method based on signal intensity characteristics of brain tissue on MT images, with and without the RF saturation pulse. During the second step, MTR values were calculated for each voxel of the brain, and during the third step, the data set of MTR values was displayed as an MTR histogram. The second and third steps were fully automated, requiring no operator interference. The amount of MT was quantified by calculation of the MTR, defined as follows: MTR = [1 - (Ms / M0)] × 100(%) M0 and Ms represent the signal intensity of an area with the saturation off and on, respectively. This ratio indicates the percentage loss of signal intensity attributable to MT. Histograms were normalized by dividing by the total number of voxels contained therein. Voxels were included in the histograms if they had MTR values > 5% (voxels with an MTR < 5% were presumed to represent CSF or noise in the absence of signal). The following parameters were computed from this histogram: the peak height of the histogram and the peak location (MTR value corresponding to the peak). Between pre- and post-chemotherapy scans, the peak height and the peak location were analyzed using paired t-test.

RESULTS

Peak height value and peak location value of all 10 patients are shown in table 1. Peak height was significantly lower in post-chemotherapy scans than in pre-chemotherapy scans ($p = 0.002$, Figure 1). Peak location didn't show significant difference between pre- and post-chemotherapy scans ($p = 0.6$, Figure 2). No abnormal signal area was noted on conventional T1-, T2-weighted or FLAIR images on either pre- or post-chemotherapy MR scan.

DISCUSSION AND CONCLUSION

In the present study, post-chemotherapy scans showed significant peak height decrease of the whole brain MTR histogram compared with pre-chemotherapy scan. Conventional MR imaging did not show any abnormal signal in white matter either before or after chemotherapy. The peak height value of MTR histogram has been thought to reflect the amount of remaining normal brain parenchyma or volume of myelinated white matter [6, 7]. In the present study, decrease of MTR histogram peak height value may show loss of myelination due to damage of oligodendroglial cells or astrocytes related to MTX chemotherapy. By normal developing process, parameters of whole brain MTR histogram analysis show peak height value decreases with peak location value increase with age, especially in young-aged (< 2 years-old) children [8]. Among these parameter changes, the increase of the peak location value over time could be attributed to the process of increasing myelination [9]. However, the decrease of the peak height value in young-aged children reflects another phenomenon [8]. Relatively homogeneously unmyelinated newborn baby brain shows high and narrow MTR histogram peak. This high and narrow MTR histogram peak decreases and widens by regionally heterogeneous myelination process [8]. This regional heterogeneity in myelination is accompanied by a regional heterogeneity in MTR values in the developing brain and adult brain [9, 10]. Thus, the decrease of MTR histogram peak height value can be attributed to increasing heterogeneity of the myelinating brain. In the present study, the peak height value decreases, but the peak location value did not show increase as seen in the normal brain myelination process. The changes in MTR histogram parameters in the current study thus do no likely represent normal developing process. In conclusion, MTR histogram analysis can show MTX chemotherapy-related subtle white matter change in ALL patients, which may have clinical implications for prevention of CNS side effects.

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Table 1

Results of MTR histogram analysis

	Before MTX		After MTX	
No.	Peak height	location	Peak height	location
1	0.10925	23	0.1014	22
2	0.12735	20	0.10301	21
3	0.09031	23	0.083	24
4	0.102237	24	0.101676	23
5	0.102439	21	0.083426	23
6	0.09856	23	0.09017	24
7	0.10519	23	0.09914	21
8	0.0872907	20	0.0708977	21
9	0.0899603	23	0.0787764	23
10	0.0900523	22	0.058694	22

Figure 1

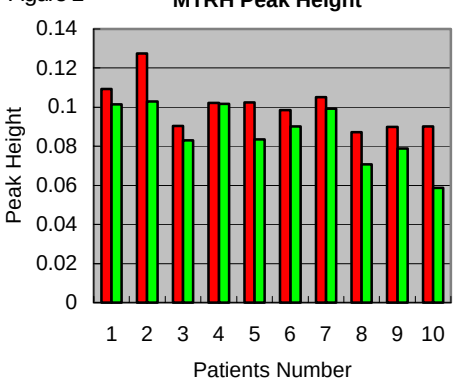

Figure 2