Treatment Effect on Delay in Growth of Superior Frontal Lobe in Childhood Acute Lymphoblastic Leukemia

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INTRODUCTION: Childhood Acute Lymphoblastic Leukemia (ALL) is the most common type of childhood cancer. Recent advances in increasingly effective treatments for pediatric ALL have improved the survival rate, however, side effects of treatment have become an important focus of investigation. Chemotherapy-induced neurotoxicity is suspected as the cause of the cognitive deficits[1-2] but mechanisms and locations of such pathophysiology are still elusive. Our research was to investigate the long-term effects of chemotherapy on the cerebral structural alterations and plasticity. We hypothesized that neurocognitive deficits in ALL might be associated with late brain development in white matter regions, in particular, frontal lobes. We studied brain anatomic images of young children with ALL who were treated with prophylactic CNS-directed chemotherapy only without cranial radiation. For the reliable measurement of brain volumes, we developed a robust segmentation procedure by combining voxel-based whole brain segmentation technique with atlas-based local masking method.

METHODS: Our study design included developmental cohorts who varied in time since diagnosis and completion of treatment. Participants included 27 children with ALL and 9 age-matched normal controls (14.0 ± 2.3 yrs., 3 female, 6 male). ALL patients consisted of 3 cohorts: cohort I (13.1 ± 3.8 yrs., 3 female, 6 male) who had been receiving maintenance therapy for 1-3 yrs. after diagnosis, cohort II (13.2 ± 3.3 yrs., 3 female, 6 male) and cohort III (13.2 ± 2.2 yrs., 4 female, 5 male) who had completed therapy for 3-5 yrs. and >5 yrs., respectively. The cumulative dosage of the chemotherapy agents did not differ among the three cohorts. It is worthy to note that there was no significant difference in age and gender between all groups. The careful control of confounding variables of age and gender is of critical importance for the reliable statistical analysis in this study since the white matter volumes is still increasing during childhood and is different between genders.

For volumetric measurement, high-resolution T_1-weighted images (3D-MPRAGE, TR/TE/FA= 2300 ms/2.98 ms/9°, isotropic 1mm voxel) were obtained on 3T human scanner (Magnex/Siemens). T_1 images were first segmented into the gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF) using VBM8 [3]. The segmented images were spatially normalized to MNI-T_1 template by applying a linear affine transformation [4] to eliminate confounding effects of brain size. Finally, white matter parcellation maps (WMPM) [5] was used to extract the volume information of individual regions of interest (Fig. 1). One-way analysis of variance (ANOVA) was used to compare mean differences of brain volume for all groups. Statistical significance was set at $p < 0.05$ with Bonferonni correction for the multiple comparisons.

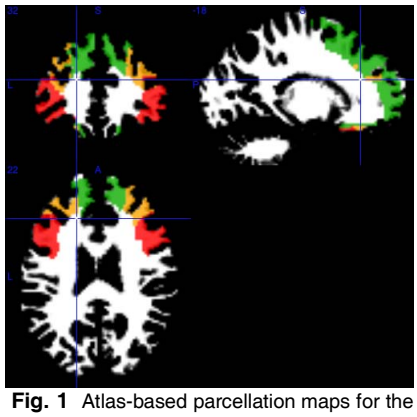

Fig. 1 Atlas-based parcellation maps for the frontal lobe (color) superimposed onto the segmented white matter image from a representative subject. Each color represents one of three identified regions within the frontal lobe: superior frontal lobe (SFL, green), middle frontal gyrus (MFL, orange), and inferior frontal lobe (IFL, red).

RESULTS & DISCUSSION: We investigated volumetric differences among four cohorts using the atlas-based volumetric mapping instead of applying voxel-based volume comparison method that is vulnerable to false positive results due to registration errors [6]. Figure 1 shows that segmented white matter images were well overlapped with three frontal lobe regions: the superior frontal lobe (SFL), middle frontal gyrus (MFL), and inferior frontal lobe (IFL). They provided reliable measurements of local brain volumes. In addition, we observed structural asymmetric patterns in the frontal lobe regions of SFL and MFL (right > left) in all groups (Fig.2), which is consistent with the previous study [7].

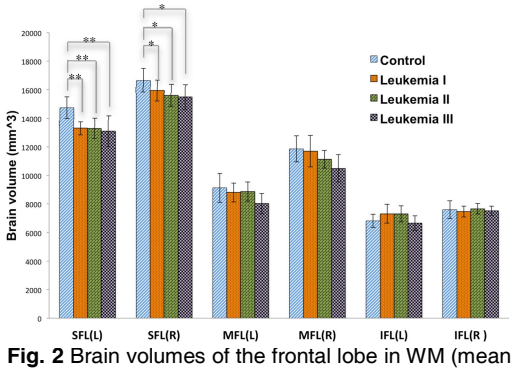

Fig. 2 Brain volumes of the frontal lobe in WM (mean ± SD). SFL: superior frontal lobe, MFL: medial frontal lobe, IFL: inferior frontal lobe, L: left, R: right.
** $p < 0.01$, * $p < 0.05$

Our volumetric analysis uncovered a significant decrease in bilateral WM volume of the superior frontal lobe in all ALL cohorts compared to controls (corrected $p < 0.01$, Fig. 2). However, there was no significant difference in any gray matter regions of frontal gyrus (data not shown herein). This morphologic finding is consistent with previous studies [1,2] and suggests both a more acute and perhaps more enduring treatment effect of prophylactic CNS–directed chemotherapy on SFL in the white matter. The maturation and growth of regional WM in the frontal lobe, plays vital roles in cognitive development. Thus, WM volume loss (or developmental delay in its growth) in the superior frontal lobe has been tightly linked to deficits in attention, working memory, academic achievement and intelligence [1-2]. Our data provides important insight for identifying an affected brain region (SFL) common to ALL cohorts at various time intervals after the treatment with converging methods of analysis. Longitudinal studies and larger sample sizes are needed to further explicate and confirm longer-term sequela.

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