A computer-aided diagnosis for detecting therapy-induced leukoencephalopathy in young patients

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Purpose: Therapy-induced leukoencephalopathy (LE), a hyperintensity of white matter on T2 and FLAIR imaging, is a possible neurotoxicity from intravenous high dose methotrexate (IV-HDMTX) in children treated for acute lymphoblastic leukemia (ALL). Radiological interpretation can have high inter- and/or intra-reader variability for differentiating these subtle changes due to its nearly identical MR properties and location with unmyelinated white matter (WM). The purpose of this study was to use objective quantitative MR imaging to create a computer-aided diagnosis (CAD) tool to prospectively assess if WM changes represent LE or normal maturational processes in these young patients.

Method: Signal intensity changes, normalized within each examination, were evaluated for children treated for ALL on a single institutional protocol. All MR imaging was performed without contrast on a 1.5-T (Siemens Medical Systems, Iselin, NJ) whole-body imager. Patients underwent a clinical imaging protocol after informed consent had been obtained from the patient, parent, or guardian, as appropriate. MR imaging sets included T1-weighted (TR/TE/TI = 8000/29/300 ms), PD- and T2-weighted (TR/TE1/TE2 = 3500/17/102 ms), and FLAIR (TR/TE/TI = 9000/119/2470 ms) sequences. Imaging was collected for 203 children aged 1.0-18.9 (median 5.8) years at time of protocol enrollment for two time points: near baseline after one course of IV-HDMTX (n=190), and after all five courses of IV-HDMTX (n=168). A combined imaging set consisting of the four MR images and WM, gray matter and CSF a priori maps from a spatially normalized atlas were analyzed with a neural network segmentation based on a Kohonen Self-Organizing Map [1] after registration and RF correction. Segmented maps were manually classified to identify the most hyperintense WM region and the normal appearing genu region, and a signal intensity difference measure was computed to normalize the data to the genu value of each examination. Age and the four MR signal intensity differences were then used to develop a CAD tool to distinguish LE from unmyelinated WM. An unsupervised hierarchical clustering algorithm with the agglomeration method of McQuitty [2] was applied to the first examination with the assumption that most examinations would not show LE at that point in therapy. A C-support vector machine (C-SVM) [3] was trained using the results from the hierarchical clustering technique to classify data as representing normal WM or LE. The accuracy of the C-SVM classification was compared to the readings of two expert observers.

Results and Discussions: Data combined from both examinations is shown graphically in Figure 1. The hierarchical clustering estimated an LE incidence rate of 26.3% (50 / 190) for the first examination compared to 26.8% (51 / 190) by the experts. For the second examination, 47.6% (80 / 168) of the examinations were labeled as LE by the C-SVM and 46.4% (78 / 168) by the experts. The overall accuracy of the CAD tool was 83.5% (299 / 358) with sensitivity to normal WM of 86.9% (199 / 229) and specificity to LE of 77.5% (100 / 129). Figure 1 shows more separation between LE and normal labels in the T2 difference for older patients, which is consistent with the presence of less unmyelinated WM and more severe LE.

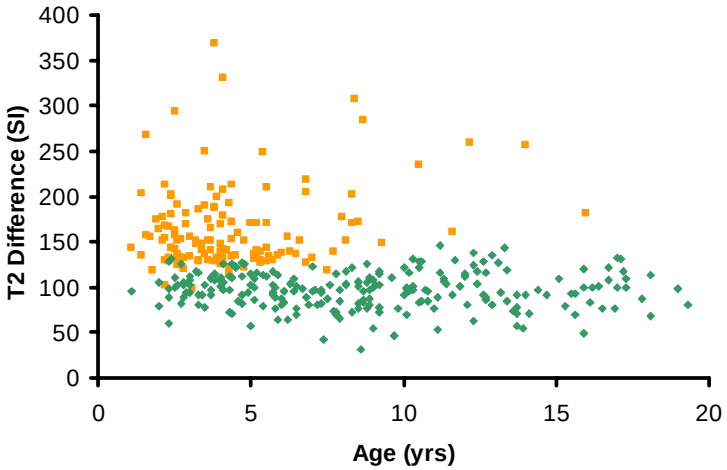

Figure 1 – Distribution of the T2 signal intensity difference values and age. Green diamonds show data labeled as normal WM by the CAD tool and orange diamonds represent LE. The plot demonstrates the influence of age on the T2 signal intensity distribution and the subsequent separation of the LE and normal labels.

Conclusion: Subtle therapy-induced leukoencephalopathy can be objectively and reproducibly detected in children treated for cancer using this computer-aided detection approach based on relative differences in quantitative signal intensity measures normalized within each examination.

References: 1. Glass JO, MRM 52, 2004. 2. Murtagh F Multidimensional Clustering Algorithms in *COMPSTAT Lectures 4*. 1985. 3. Schölkopf B *Learning with kernels*. 2002.