Pediatric ALL: Characterization of WM Damage and Associated Risk Factors

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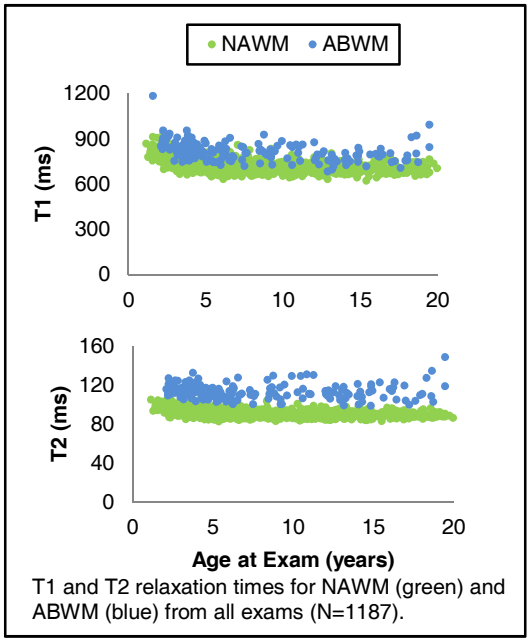
PURPOSE: The most common form of pediatric cancer is acute lymphoblastic leukemia (ALL), diagnosed in 3000 U.S. children annually. While methotrexate (IV-MTX), administered intravenously at high doses, has increased the 10-year survival rate for pediatric ALL patients to ~91% [1], MR neuroimaging studies reveal leukoencephalopathy (LE), the most common neurotoxic side effect during the course of therapy. LE, viewed as T2W white matter (WM) hyperintensities, may be transient or chronic [2]. Neurocognitive deficits resulting from LE in ALL patients can have a devastating effect on quality of life, long term [3]. The purpose of this study was to objectively assess influence and risk factors for LE in pediatric ALL.

METHODS: Pediatric ALL patients (N=377; ages: 1-18 years; 207 males) enrolled on our institutional ALL protocol were assigned to low- (LR) or standard-high-risk (SHR) groups based on comprehensive risk classification. Patients were treated with seven courses of IV-MTX (dose: 2.5 g/m^2 LR, 5.0 g/m^2 SHR), hydrocortisone, and cytarabine, but no cranial irradiation [4]. Patients underwent MR imaging at four time points during therapy: MR1 (week 6, induction), MR2 (week 7, continuation), MR3 (week 31, continuation), and MR4 (week 120 of continuation). LE diagnosis was given for each of 1220 total MR exams by a clinical radiologist. All images were 4-mm-thick contiguous axial sets collected on a 1.5-T Vision whole-body unit (Siemens Medical Systems, Iselin, NJ). The MRI protocol included a T1-W multi-echo inversion-recovery sequence (TR=8000, TE=27ms, TI=300ms, NEX=1, 7 echoes), a FLAIR multi-echo sequence (TR=9160ms, TE=109ms, TI=2400ms, NEX=1, 21 echoes), and a dual spin-echo sequence to acquire proton-density and T2-W images simultaneously (TR=3500ms, TE1=14ms, TE2=101ms, NEX=1). Using an automated segmentation routine based on artificial neural networks tissue maps were obtained [5]. Two quantitative images were also acquired: T1-W (TR=2500ms, TE=68ms, TI=900, NEX=1) and T2-W (TR=2000ms, NEX=1, 16 echoes sampled every 22.5ms). Normal appearing (NAWM) and abnormal appearing white matter (ABWM) volumes, as well as T1 and T2 relaxation rates were quantified longitudinally and at individual MR time points. To assess influence and risk factors for LE in pediatric ALL, interactions between neuroimaging measures, demographic factors, and clinical covariates (age, sex, risk group/IV-MTX dose, LE presence at each MR time point, and long term LE status: transient or chronic) were statistically investigated.



T1 and T2 relaxation times for NAWM (green) and ABWM (blue) from all exams (N=1187).

RESULTS: LR (N=188, 88 males) and SHR (N=189, 120 males) groups were significantly different by age (LR: 5.1±3.2; SHR: 8.8±5.0; d=0.89, p<0.0001). LE prevalence was assessed at MR2 (22.0%) compared to MR1 (7.6%) in 250 patients who completed both scans, and at MR4 in all patients (N=306, 12.7%). Risk factors for increased prevalence were sex (+12.7% M>F, p=0.015) and risk group (+5.8%, SHR>LR). LE Resolution was examined by subtracting LE prevalence at MR4 from MR2 (9.0%), in 277 patients who completed both scans. Increased resolution was influenced by factors of sex (+6.6%, M>F) and risk group (+6.2%, LR>SHR, p=0.001). Of the 377 patients enrolled, those diagnosed with chronic LE (CLE; N=39, 25 males; age=8.5±5.1) were significantly older than those with transient LE (TLE; N=34, 21 males; age=5.9±4.6; p=0.008) Further, age is significantly different between all three groups, where TLE<Normal<CLE (X^2=7.8, p=0.020). Quantitative T1 and T2 relaxation rates of NAWM were evaluated in 1187 of the exams of which 176 had measureable regions of ABWM or LE. Average T1 values across all NAWM decreased from approximately 818ms at age 1 year to approximately 707 at age 20 years, while average T2 values decreased from 97ms to 89ms, respectively. T1 and T2 relaxation rates were significantly longer in ABWM versus NAWM (T1: ABWM=817±66ms, NAWM=730±42ms, p<0.0001; T2: ABWM=114±9ms, NAWM=92±4ms, p<0.0001), but were not significantly influenced by age. Longitudinal changes in the extent (proportion of WM) and intensity (elevation in relaxation times relative to NAWM) were evaluated in CLE versus TLE patients. At MR 2, the extent of WM was significantly greater in CLE (N=28) versus TLE (N=23) patients (CLE: 11.4±7.3, TLE: 7.0±5.4; p=0.009). At MR3, the intensity of T1 was significantly higher in CLE (N=32) versus TLE (N=12) patients (CLE=78±48, TLE=43±36; p=0.023).

CONCLUSIONS: Factors of increased age and male sex are the biggest predictors for a standard or high risk diagnosis and chronic LE, while T2 relaxation rates help differentiate normal from abnormal WM tissue. The extent of LE and LE intensity of T1 are greater in chronic LE patients. Future work should address the influence of identified risk factors and neuroimaging measurements on neurocognitive impairment in pediatric ALL patients receiving HD-MTX.

REFERENCES:

1. Pui, CH et al. Semin Hematol. 2013.; 2. Shuper A et al. Isr Med Assoc J. 2002.; 3. Conklin HM et al. J Natl Cancer Inst. 2012.; 4. Pui CH et al. N Engl J Med. 2009.; 5. Reddick WE et al. Neuroradiology. 2007.