Published in final edited form as:

Neuroradiology. 2007 November ; 49(11): 889–904.

Quantitative morphologic evaluation of magnetic resonance imaging during and after treatment of childhood leukemia

Wilburn E. Reddick[✉], Fred H. Laningham, John O. Glass, and Ching-Hon Pui

Division of Translational Imaging Research (MS #210), Department of Radiological Sciences, St. Jude Children's Research Hospital, 332 N. Lauderdale Street, Memphis, TN 38105-2794, USA (W. E. Reddick, J. O. Glass); Division of Diagnostic Imaging, St. Jude Children's Research Hospital, Memphis, TN, USA (F. H. Laningham); Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA (C.-H. Pui)

Abstract

Introduction—Medical advances over the last several decades, including CNS prophylaxis, have greatly increased survival in children with leukemia. As survival rates have increased, clinicians and scientists have been afforded the opportunity to further develop treatments to improve the quality of life of survivors by minimizing the long-term adverse effects. When evaluating the effect of antileukemia therapy on the developing brain, magnetic resonance (MR) imaging has been the preferred modality because it quantifies morphologic changes objectively and noninvasively.

Method and results—Computer-aided detection of changes on neuroimages enables us to objectively differentiate leukoencephalopathy from normal maturation of the developing brain. Quantitative tissue segmentation algorithms and relaxometry measures have been used to determine the prevalence, extent, and intensity of white matter changes that occur during therapy. More recently, diffusion tensor imaging has been used to quantify microstructural changes in the integrity of the white matter fiber tracts. MR perfusion imaging can be used to noninvasively monitor vascular changes during therapy. Changes in quantitative MR measures have been associated, to some degree, with changes in neurocognitive function during and after treatment

Conclusion—In this review, we present recent advances in quantitative evaluation of MR imaging and discuss how these methods hold the promise to further elucidate the pathophysiologic effects of treatment for childhood leukemia.

Keywords

Acute lymphoblastic leukemia; MR imaging; Drug effects; Neurotoxicity

Introduction

With improved treatment outcome in children with cancer, current emphasis is placed on the survivors' quality of life, including neurocognitive function. Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, affecting 2,400 children annually in the United States. The 5-year event-free survival estimate for pediatric patients with ALL is approaching 90% [1]. Methotrexate (MTX) given intravenously (IV-MTX) at a high dose decreases the likelihood of hematologic, testicular, or central nervous system (CNS) relapse. However, MTX has a substantial toxic effect on the CNS and can lead to severe neurologic morbidity. Leukoencephalopathy (LE), which is seen as white matter (WM) hyperintensity on T2-

[✉]e-mail: gene.reddick@stjude.org URL: <http://www.stjude.org/reddick>

Conflict of interest statement We declare that we have no conflict of interest.

weighted magnetic resonance (MR) images (as seen in Fig. 1), is the most common manifestation and may be either persistent or transient [2]. The frequency and severity of LE depends on MTX dose, cumulative exposure, or other clinical variables.

Treatment for pediatric ALL must include treatment of the CNS to eradicate occult CNS leukemia. Historically, the most common methods of CNS prophylaxis include intermediate- to high-dose IV-MTX, with or without cranial or craniospinal irradiation. More recently, efforts to eliminate irradiation from the treatment of ALL and thus prevent adverse neurologic and neuropsychologic effects have prompted the use of more intensive CNS-directed chemotherapy. Some researchers have argued that MTX in high doses may protect the CNS in some circumstances [3]. However, IV-MTX therapy in high doses is associated with neurotoxicity and that MTX-induced neurotoxicity is a clinically relevant problem in pediatric oncology.

We review here the pathophysiology caused by chemotherapy for childhood ALL. We also summarize the evolution of MR imaging and discuss the contemporary MR imaging methods used to evaluate the adverse neurologic and neuropsychologic effects experienced by pediatric patients being treated for ALL and by long-term survivors of the disease.

Pathophysiology

MTX can induce reversible LE by inhibiting the turnover of myelin lipids and proteins. This inhibition results in intramyelinic splits and intralamellar formation of vacuoles in which interstitial fluid can accumulate [4]. The plasma concentration of homocysteine (or homocysteic acid) may be related to IV-MTX treatment, neurotoxicity, or both [5]. One possible mechanism of this relationship is a relative deficiency in methylene tetrahydrofolate reductase, which predisposes children to hyperhomocysteinemia [6], and has been hypothesized to predispose them to IV-MTX neurotoxicity [7]. The resulting inhibition of myelin turnover and increase in free water content would greatly affect both the T1 and the T2 relaxation times of the tissue, and such effects would change the contrast on the image. This effect is demonstrated in Fig. 2 for both conventional T2-weighted imaging and quantitative maps of T1 and T2 relaxation times.

The mechanisms of ALL treatment-induced neurotoxicity remain unclear. Damage to two components of the CNS, i.e. oligodendrocytes and the vasculature, may contribute to the atypical development of WM volume in childhood ALL survivors. Iron contained in oligodendrocytes plays an important role in myelogenesis and the maintenance of the myelin sheath [8], and proton magnetic relaxation times vary as a function of iron concentration [9]. Atypical WM volume development and WM hyperintensities observed in previous studies could be explained by demyelination, which is caused by damage to oligodendrocytes. This explanation is consistent with the destruction of oligodendrocytes observed over 30 years ago by Smith who conducted a post-mortem study of patients with leukemia treated with MTX [10].

Ischemia, which is induced by damage to the microvasculature, is another possible mechanism for atypical WM volume development. MTX inhibits dihydrofolate reductase, which is an enzyme involved in the biosynthesis of folic acid coenzymes; therefore, MTX reduces folate. A reduced folate concentration results in an elevation of the level of homocysteine, which is toxic to the vascular endothelium and may induce ischemic side effects [7]. This mechanism is consistent with the hyperintensities observed in patients during antileukemia therapy. Hyperintensities have been observed in deep WM, extend from the frontal and occipital lobes to the subcortical nuclei and superior longitudinal fasciculus. The deep WM is most vulnerable to ischemic changes because of the sparse vascularity in that region [11].

MTX is not the only drug used in the treatment of ALL which can have an effect on the morphology of the developing brain [12]. Other drugs such as asparaginase may produce deficiencies of antithrombin III, plasminogen, and fibrinogen which could result in cerebrovascular disease, especially venous sinus thrombosis. Corticosteroids, used extensively in the treatment of ALL, also have a pronounced effect on cerebral morphology, resulting in transient cortical atrophy as evidenced by the widening of the sulci accompanied by increases in the volume of cortical cerebrospinal fluid (CSF).

Early attempts to quantify imaging changes

Before 1990, computed tomography (CT) examinations were used to investigate LE in patients with ALL who were treated with intrathecal MTX (IT-MTX) and radiation [13-17]. These early studies used quantitative measures of ventricular size and WM density as well as qualitative assessment for intracranial calcifications to determine the prevalence of LE in their patient populations. The prevalence of LE ranged from 9% to 35% (median 22%), depending on when the evaluations were performed. After completion of therapy, prevalence typically increased substantially, ranging from 16% to 69% (median 35%) [13-17]. We did not include the study by Chu et al. [18] in these reported ranges, because that study included only three subjects. Although CT examinations are still used in some institutions, they are increasingly being replaced by MR imaging [18-24].

In contemporary protocols, efforts to avoid the adverse neurologic and neurocognitive effects have prompted the reduction or elimination of radiation and the intensification of IT and IV chemotherapy [4,15,17-19,21-27]. In these studies, many patients were evaluated by MR imaging. Once again, the prevalence of LE varied according to the time of evaluation: at baseline and at the beginning of consolidation chemotherapy, prevalence was 0%; during therapy, 18% to 76% (median 38%); and after completion of therapy, 5% to 53% (median 20%). Because of differences in diagnostic imaging and systemic and IT chemotherapy, the prevalence of LE in patients treated on early protocols and those treated on contemporary ones cannot be meaningfully compared.

IV-MTX therapy, like irradiation, has been associated with acute and chronic neurotoxicity. However, interpreting the results of clinical studies is complicated by the variation in systemic MTX exposure [14,16,28-30]. Acute events associated with IV-MTX, with or without irradiation, include seizures and transient neurologic abnormalities such as focal sensorimotor deficits, and acute mental status changes occur in 5% to 10% of patients [31-35]. In the large Pediatric Oncology Group (POG) 9005 study approximately 8% of patients experienced acute clinical neurotoxicity after IV-MTX treatment alone; 75% of those patients with symptoms of neurotoxicity had qualitative MR imaging evidence consistent with a diagnosis of LE [27].

Most recent protocols that have included IV-MTX treatment have routinely used MR imaging to qualitatively evaluate neurotoxicity. In these studies, the degree of LE was rated on a subjective grading scale. Some studies [4,18,23] used a variant of the original scale proposed by Wilson in 1991 [25]. In these studies, grade 0 indicated a normal examination, grade 1 corresponded to mild changes that did not extend to the gray matter-WM (GM-WM) junction (0-25% WM involvement), grade 2 indicated moderate changes extending to the GM-WM junction (25-50% WM involvement), and grade 3 was reserved for severe changes that involved the GM-WM junction and were continuous throughout the centrum semiovale (more than 50% WM involvement).

Other early studies only classified neuroimaging of patients as normal, probably abnormal, or definitely abnormal, and did not assess the extent of WM involvement [20,24]. None of these early studies evaluated intra- and interobserver variance. This subjective grading precluded the

across-study comparison of therapy-induced LE and did not provide any continuous measure of the intensity or extent of LE as a function of other influential factors.

Computer-aided detection of leukoencephalopathy

There are no universal guidelines to differentiate subtle LE from normal developmental changes. LE can vary in duration, extent, and intensity. Although focal lesions are easily identified, subtle changes often do not have distinct boundaries with the normal-appearing WM, especially the normal terminal zones of myelination. Unmyelinated WM regions are also slightly hyperintense on T2-weighted images [36], an important consideration in a patient population with a peak age at diagnosis between 2 and 5 years [37]. Therefore, these MR properties make reliably identifying subtle therapy-induced LE in children treated for ALL a challenging task. In 2006, we reported the feasibility of developing a computer-aided detection (CAD) tool to assist in identifying therapy-induced LE in young children during therapy for ALL [38]. We used a neural network segmentation algorithm based on a Kohonen Self-Organizing Map (SOM) to analyze a combined MR imaging set consisting of T1-weighted, T2-weighted, PD-weighted, and FLAIR images and proportional volume maps (from a spatially normalized atlas) showing WM, GM, and CSF. The segmented maps were manually classified to identify the most hyperintense WM region and the normal-appearing genu region. Signal intensity differences that were normalized to the genu within each examination were generated for four time points in 228 children. We combined the differences in signal intensity from these regions on multispectral MR imaging sets with age at examination to provide a possible quantitative measure for decision making. A second SOM was then trained on examinations performed at baseline and applied to all subsequent examinations of the patients.

To evaluate the performance of the CAD tool, we compared each label to manual readings of each examination. Manual readings were done by two trained observers to determine if LE was present in any image of the examination. To reduce variability, both observers viewed the data at the same time. The differentiation criteria required that LE have higher signal intensity than the adjacent cortical GM. To evaluate the reproducibility of this manual reading, we randomly repeated 50 examinations and measured the agreement using a Kappa index. The overall agreement between the CAD tool and the consensus reading of the two trained observers was 84.1% (535/636); agreement in the training set was 84.2% (170/202); and that in the testing set was 84.1% (365/434).

These results suggest that the CAD tool can objectively and reproducibly detect subtle therapy-induced LE in young children. Unfortunately, because the CAD tool is based on signal intensity differences, variations in magnets, coils, and sequences require that individual CAD tools be established for each institution and imaging protocol. A more generalizable processing and decision model is still needed.

Segmenting normal and abnormal tissue volumes

The MR imaging characteristics of LE are similar to those of other diseases (e.g., multiple sclerosis, MS) or processes (e.g., aging) that cause WM hyperintensities. Several modifications to existing methods have been recently reported for quantitative analyses of WM hyperintensities. Region-growing techniques with a variety of automated and semiautomated stopping criteria have been utilized [39-41]. These techniques are limited by multiple factors: the degree of local intensity contrast necessary between the lesion and surrounding tissues; the single-imaging type, and the much higher level of operator expertise required for subjective selection of each lesion on every slice of the imaging set.

Ashton et al. [39] analyzed multispectral data with a model-based method to identify lesions in patients with MS. Their technique made assumptions about the model and possible variance in the model. Other groups have recently reported modifications to the k-nearest neighbor technique to improve lesion identification and localization in geriatric populations and patients with MS [42-44]. The k-nearest neighbor technique is sensitive to intensity inhomogeneities and relies on either assumptions of intensity distributions or subjective samples to define the distributions. Wei et al. [42] found that the addition of template-driven segmentation to the expectation-maximization segmentation and partial volume correction algorithms significantly improved the accuracy and reliability of WM signal abnormality measures.

Encouraged by the success of Wei et al., we recently examined whether the previously reported method for quantitatively assessing LE in patients with ALL could be improved [45]. We analyzed multispectral MR images from 15 children treated for ALL and compared three different analysis techniques to examine improvements in the segmentation accuracy of LE versus manual tracings by two experienced observers. The original technique used a WM mask based on the segmentation of the first serial examination of each patient and not on a priori information [46]. The first modified technique combined spatially normalized a priori maps as input and a two-dimensional gradient-magnitude threshold and the second used a three-dimensional threshold. MR images were segmented with a Kohonen SOM for all three algorithms. Kappa values were compared for the three techniques to each observer, and statistically significant improvements were seen between the original and third algorithms (*observer 1* 0.651, 0.744, $P=0.015$; *observer 2* 0.603, 0.699, $P=0.024$). While the new WM mask and two-dimensional gradient-magnitude threshold improved the results, the best results were seen when the gradient magnitude threshold was modified to three dimensions. The results of this type of quantitative morphometric processing are shown in Fig. 3.

A possible error source in using these new algorithms is the selection of an adult atlas. Although Wilke et al. reported errors in using adult atlases to evaluate pediatric cases [47], the threshold values that were empirically determined to create the WM mask may have corrected some of the errors. Another potential concern with this newly proposed algorithm lies in its ability to perform spatial normalization. Misalignment of the a priori maps could translate into misclassifications. We performed spatial normalization with the Statistical Parametric Mapping (SPM) 2 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). As with any image processing that uses a registration-based technique, this error must be minimized to ensure quality data and quantitative results.

Another more recent form of nonlinear registration of local deformations has been achieved using a free-form deformation (FFD) based on B-spline interpolation [48]. The deformation field is determined by the displacements specified on these control points, and the displacements off the control points are interpolated based on the neighborhood control points using B-splines. The resolution of a control lattice specifies the degrees of freedom. A control lattice with small spacing allows modeling of highly local deformation such as ventricles in a patient with hydrocephalus. However, increasing the degrees of freedom not only improves flexibility but also increases the computational complexity. A hierarchical multiresolution approach was employed to achieve a good trade-off between spatial normalization accuracy and the associated computational cost. To constrain the FFD transform, Wahba introduced a penalty term to regularize the transform [49]. Our experience with the FFD approach to nonlinear registration of patients treated for posterior fossa brain tumors has shown that removing extrameningeal tissues, cerebellum and brain stem from the images before registration allows better registration of the cerebrum [50].

Prevalence of leukoencephalopathy

In a recent quantitative MR study, we examined the longitudinal prevalence of LE in children treated for ALL on a single institutional protocol, which included seven courses of IV-MTX and multiple-agent IT therapy with MTX, hydrocortisone, and cytarabine, but no irradiation [51]. Due to both the limited sample size and the consistency of IT therapy and steroids across all subjects, these factors were not considered influential covariates in this study. Instead, we assessed sex, MTX dose, and age at diagnosis as possible risk factors affecting the prevalence of LE. LE was detected using an objective, quantitative MR imaging approach. The prevalence of LE in this study was then compared and contrasted with that found in previous studies to objectively assess the influence of risk factors on the temporal pattern of LE in patients who were treated for ALL but did not receive irradiation.

Consecutive patients who were at least 1 year of age and had enrolled on our institutional ALL treatment protocol between 30 July 30 1998 and 30 August 30 1999 were eligible for the study. Because the study was designed to assess the longitudinal prevalence of LE in otherwise normal-appearing brains, patients with other neurologic complications such as thrombosis were not eligible. Altogether, 45 patients were eligible for this study: 21 male and 24 female, aged 1.5 to 18.6 years at diagnosis (median 5.4 years). Quantitative preprocessing and MR image analysis were performed for CAD of LE.

Increasing exposure corresponding to more courses and higher doses of IV-MTX was associated with an increased prevalence of LE. Patients in the standard- and high-risk ALL groups received twice the dose of IV-MTX and had a higher risk of LE than those in the low-risk ALL group. However, even patients in the low-risk group had a 67% probability of LE after seven courses. All of the patient groups demonstrated a significant increase in the prevalence of LE after four courses of IV-MTX, and the prevalence in the standard- and high-risk groups increased further with the additional three courses of IV-MTX. However, the prevalence of LE reduced by almost half during the period between the completion of IV-MTX and the end of therapy for both patient groups. This finding suggested that LE is mostly transient, and its prevalence may continue to decrease with longer follow-up. Although the magnitude of results in this study may be specific to this treatment protocol, the transient longitudinal pattern and the effect of covariates (predictors) should hold in other studies using IV-MTX to treat children with ALL.

Prevalence of LE in our study can be compared and contrasted with that seen in previous studies of patients treated for ALL with IV-MTX and IT-MTX prophylaxis under the constraint that the systemic therapy regimens are not identical. Both Wilson et al. [25] and Chu et al. [18] reported no prevalence of LE at the beginning of consolidation therapy 8 weeks after diagnosis of ALL, whereas we observed a 16% prevalence [51]. The regions of LE were subtle and diffuse, and the increased sensitivity in detection of these regions was most likely due to the objective, quantitative approach. The second time point, at the beginning of continuation therapy, demonstrated an overall 59% prevalence, which is almost identical to the 60% reported by Wilson et al. [25]. However, more recent studies by Asato et al. [4], Paakko et al. [21], and Chu et al. [18] have shown prevalences of 21% to 38%. The prevalence of LE in our study after all seven courses of IV-MTX at week 37 of continuation therapy was 76%, which was identical to that reported by Mahoney et al. [27] 1 year after diagnosis and was comparable to the prevalence of 52% reported by Wilson et al. [25] also 1 year after diagnosis. None of the earlier studies included data that could be compared with our fourth time point. Although the results at any individual time point in our study were comparable to those from previous studies, ours was the first to use objective quantitative MR measures to assess the longitudinal pattern of LE prevalence.

Extent and intensity of leukoencephalopathy

Building on our previous work, which examined the longitudinal prevalence of LE in 45 children (low-risk, 10 male/12 female, mean age 5.0 years at diagnosis; standard-/high-risk, 11 male/12 female, mean age 9.2 years at diagnosis) treated for ALL on a single institutional protocol without irradiation, we prospectively and objectively assessed the temporal evolution of LE and its extent and intensity in these same patients using quantitative MR imaging [52]. Assessment for the CAD and quantitation of LE was accomplished using a multispectral Kohonen SOM for tissue segmentation. Each imaging set was registered, and the intensity inhomogeneity on the MR images was corrected using a new implementation of an entropy-minimization algorithm [53]. An index section was chosen as a common starting point for the volumetric studies. This single transverse section was at the level of the basal ganglia, included both genu and splenium of the corpus callosum, and generally showed the putamen and the lateral ventricle. Two sections below this level and those up to the apex of the brain were included in the volumetric analyses to create a volume of interest covering most of the supratentorial brain. These sections allowed quantification of both interhemispheric and intrahemispheric WM tracts. They were also highly predictive of the full cerebral WM, GM and CSF volumes in other patient populations [54].

We quantified the volume of regional brain parenchyma on MR images by using an automated hybrid neural network segmentation and classification method [55]. The resulting classified regions were mapped to a color scheme, and a histogram was then completed for each color to determine the number of pixels. That value was then multiplied by the pixel volume to determine the sampled volume of each tissue type. Robust reliability and validity have been established for these methods, resulting in a predicted variance of approximately 2% in the repeated measures of WM and GM [46].

Once each examination was segmented, we assessed the extent of LE and the normal-appearing WM volume for all transverse sections, from the apex of the brain to a level 6 mm below the corpus callosum. The proportion of WM affected was defined as the total volume of LE over the combined volume of LE and normal appearing WM. Quantitative T1 and T2 parametric maps were also created. These represented the relaxation times at each voxel in the image. Segmented tissue maps of the corresponding section were used to automatically identify regions of LE and normal-appearing WM. Relative LE intensity was defined as the difference between the mean T1 or T2 of LE and normal appearing WM for the same subject in the same section. Figure 4 demonstrates coregistered segmented tissue maps and quantitative relaxation maps for a child during therapy for ALL.

Increasing exposure corresponding to more courses and higher doses of IV-MTX was associated with increased intensity and extent of LE. The proportion of WM affected in both low-risk and standard-/high-risk patients increased significantly with additional courses of IV-MTX ($P<0.01$ and $P=0.05$, respectively); the intensity of LE also increased steadily. However, both the intensity and extent of LE reduced by approximately one-third between the completion of IV-MTX and the last time point for both patient groups. This finding combined with those from previous work suggests that some, but not all, LE is transient and may continue to decrease in prevalence, extent, and intensity with longer follow-up.

Voxel-based analysis

Previous studies have established the prevalence, extent, and intensity of LE in patients treated for ALL without irradiation [51,52], but an objective assessment of the regions of WM affected by LE has yet to be performed. In a recent study, we used voxel-based analyses of T2 imaging within the WM of patients after the first and final courses of IV-MTX treatment for ALL to assess which WM tracts were preferentially damaged [56]. After excluding patients with

cerebral thrombosis, cortical dysplasia, and large developmental abnormalities, 204 patients (117 male and 87 female) aged 1.2 to 18.9 years (median 5.1 years) were eligible for this study. MR imaging was performed on a 1.5-T whole-body system using the standard circular polarized volume head coil (Siemens Medical Systems, Iselin, N.J.). In each patient, 19 4-mm thick axial T2-/PD-weighted dual spin-echo images (TR/TE1/TE2=3500/17/102 ms, seven echoes) were obtained with a 1-mm gap.

Voxel-based analysis began with the creation of a custom template based on the patient cohort. First, each original image set was registered to a target normal-appearing image set selected from a patient. Registration consisted of a two-step process involving an affine transformation followed by an FFD nonlinear transformation that corrects for global differences in brain shape. With all of the image sets residing in the same stereotactic space, an average image was created. Next, a second registration was performed for each original T2 image set, with the average T2 image as the target using the same approach previously described. A WM mask was created by using SPM2 to segment the average T2 image set. Voxel-wise statistical testing was performed using SPM2. To analyze variance, F-tests were performed to determine which voxels were significantly different between examinations over the entire subject population. A *P*-value and cluster threshold was specified to limit the analysis only to regions that had significant differences between examinations and had a sufficient number of continuous voxels for analysis. These data were overlaid onto the average T2 image for visualization.

The patient cohort was separated into two age groups (<5 years, *n*=98, and ≥5 years, *n*=106) to control for the maturational differences in children. Initial analysis of each group was insensitive to regional changes within the WM and detected differences only at tissue interfaces. Within each group, patients' treatment was stratified by the radiologist's reading of the second examination as normal (70 patients <5 years, and 87 ≥5 years) or LE (28 patients <5 years, and 19 ≥5 years). Results from the voxel-based analysis of patients with an abnormal second examination are shown in Fig. 5 for each group of patients. The WM tracts in the frontal lobe were significantly altered in the sets from both younger and older patients. However, patients older than 5 years who exhibited LE also showed a significant change in their posterior WM tracts. Images from subjects who upon the second examination were classified as "normal" were also inspected for both groups and showed differences only at tissue interfaces.

This study identified common areas of T2 changes in the WM among patients who experienced LE associated with treatment for ALL. These changes occurred mainly in the WM tracts of the frontal lobe, which could be the etiology of the cognitive difficulties in this cohort. Additional changes in the posterior WM tracts in older patients may indicate a difference in susceptibility of WM with varying degrees of myelination. Maturation, growth, and organization of regional WM, specifically that in the frontal-parietal regions, play an important role in cognitive development [57]. ALL survivors exhibit a consistent pattern of deficits in attention and a long delay in memory recall. Given the locations of the WM abnormalities caused by antileukemic treatment, one might expect additional deficits in executive function to be present. Individualized, more targeted neurocognitive performance studies may further elucidate the effects of LE on the developing brain.

Long-term morphologic changes in white matter volume

While the studies discussed thus far focused on quantitative MR imaging in patients during treatment for ALL, the true impact of therapy on the developing brain may be most evident in survivors. We recently examined ALL survivors treated with either chemotherapy alone or in combination with irradiation [58]. A consistent neurocognitive testing battery was used to evaluate intellect, attention, and academic achievement. WM volumes across a transverse volume of interest encompassing the entire corpus callosum were measured quantitatively and

objectively. This study tested the hypothesis that ALL survivors with lower volumes of WM have more severe deficits in attention and learning.

Evaluations of 112 children treated at two institutions were collected. Those included in this study were initially enrolled on one of five institutional treatment protocols for patients with ALL. Patients received multiple courses of IV-MTX and multiple doses of IT therapy with MTX, hydrocortisone, and cytarabine. ALL survivors were grouped on the basis of the intensity of therapy they received, i.e. whether the patients did ($n=28$) or did not ($n=84$) receive cranial irradiation (18 Gy) in addition to chemotherapy. Only one patient had intracranial calcifications. A group of 33 healthy sibling controls 6 to 16 years old was also recruited and imaged for volumetric measures of WM, GM and CSF across the volume of interest without sedation or administration of contrast agent.

Most neurocognitive performance measures demonstrated significant deficits from normative test scores, but only the attention measures exceeded one standard deviation from normal. Measures of academic achievement differed between the two patient groups, and deficits exceeding one standard deviation from normal were seen only in patients who received irradiation. Patients treated with chemotherapy alone had significantly greater volumes of WM than those who received chemotherapy and irradiation ($P=0.02$), but WM volumes were still significantly smaller than those of age- and sex-matched healthy sibling controls ($P=0.03$). Moreover, smaller WM volumes corresponded to larger deficits in attention, intelligence, and academic achievement.

CNS toxicity attributed to treatment for ALL has been well studied. Adverse effects of therapy have been observed both after chemotherapy only and after chemotherapy combined with cranial irradiation [29]. Previous studies have recognized WM changes in survivors [23,29], and metabolic changes during antileukemic therapy have been detected with ^1H MR spectroscopy [18]. However, most conventional MR imaging studies evaluated these changes based on visual inspection of the image intensity. These studies found only a small prevalence of MR intensity abnormalities, and no correlation between neuropsychological functioning and these changes [23]. In contrast, we quantitatively evaluated WM volumes and found a significant deficit compared to age- and sex-matched controls [58]. Furthermore, we found strong correlations between the quantitative WM volumes and most neurocognitive performance measurements (attentiveness and spelling were the two exceptions), suggesting that WM volume represents a sensitive measure of neurotoxicity.

Both groups of ALL survivors demonstrated clinically significant impairment of omissions and risk-taking, two functional domains of attention. This finding is consistent with a previous study by Paakko et al. [23]. The D' (attentiveness) measure demonstrated some slight inattentiveness, which was not considered clinically significant and was only weakly correlated with WM volumes. Generally, attentiveness measures reflect the subject's ability to distinguish an object; omissions and risk-taking measures reflect the subject's ability or speed of reacting to an object. Therefore, these results showed that ALL survivors have deficits in reacting to objects rather than distinguishing objects. This finding is consistent with a recent report by Mennes et al. who found that ALL survivors treated with chemotherapy alone process information more slowly than do healthy controls, especially when more information has to be processed or when attention has to be focused precisely [59].

Object vision is received in the visual cortex and supported by parallel ventral pathways that convey information to the parietal and inferior temporal cortical areas. Retrieval of information requires recruitment of stored information into a special short-term store called "working memory," which is located in the prefrontal cortex [60]. The impaired ability to react to an object suggests that these survivors have deficits in conveying information, especially between

lobes. This hypothesis is further supported by the strong relationships between WM volume and omission and risk-taking measures. Transient hyperintensities observed during antileukemia therapy extend from the frontal, temporal, and occipital lobes to the subcortical nuclei and superior longitudinal fasciculus. These areas of hyperintensity may be precursors of later deficits in conveying information between lobes. Atypical WM volume development in these ALL survivors suggests that even transient hyperintensities seen during therapy can lead to permanent subtle WM volume changes, which would be very difficult to recognize by visual inspection.

Cranial irradiation played a significant role in treatment-related changes in WM volumes and academic achievement but not in attention or intellect. Measures of academic achievement in patients who underwent irradiation were significantly lower ($P<0.01$) than normative means. Both WM volume and academic achievement measures in patients treated with radiation were significantly lower than those in patients who did not receive radiation. However, there was no significant difference in attention measures between the two patient groups. These results suggest that patients treated with chemotherapy alone experience less WM damage and are better able to compensate intellectually and academically for their attention deficits. Patients treated with cranial radiation had more severe impairment of WM volume development and were unable to compensate, resulting in more significant deficits in learning.

Cerebral perfusion studies

Perfusion quantification using MR imaging can be divided into two categories: those that employ exogenous tracer agents and those that use water protons in arterial blood as an endogenous label. The current approach to imaging examinations of asymptomatic children during therapy for ALL is to rarely administer contrast agent; therefore, the latter perfusion technique is preferable. Magnetized water molecules in arterial blood are labeled by changing their state of longitudinal magnetization by using tagging prepulses [61-63]. This method is called arterial spin labeling (ASL) and can be accomplished with either pulsed or continuous labeling as demonstrated in Fig. 6.

Very few clinical studies have assessed cerebral perfusion in patients during and after therapy for leukemia. In one early study of 25 children treated for ALL (13 cranial irradiation, 12 IV-MTX and IT-MTX only), Harila-Saari et al. [64] performed brain single photon emission CT (SPECT), cerebral MR imaging, and neurologic and neurocognitive assessments at the completion of therapy. Of the 12 patients, 8 (75%) who did not undergo irradiation had brain perfusion deficits on SPECT images. Only one patient exhibited WM changes on conventional MR imaging, but no previous MR examinations done during therapy were available. Impairment of neurocognitive functioning was found in 86% of patients studied, but no significant differences were seen between patients who had deficits and those who did not. However, only intelligence tests were used for this assessment. Another small study around the same time, used SPECT to evaluate six patients during treatment for leukemia; all six showed deficits [65]. This finding was supported by data from a slightly larger study in which 9 of 12 patients (75%) showed cerebral perfusion deficits during antileukemia therapy [66].

A more recent study by Paakko et al. [67] compared perfusion MR imaging and SPECT in 19 patients treated for ALL (9 patients were at the end of therapy, and 10 were 4-8 years after therapy). Only 17 of the patients had SPECT examinations. SPECT perfusion deficits were detected in five of ten patients whose antileukemia therapy did not include cranial irradiation (two were imaged at the end of therapy, and three were imaged years after therapy). Four of the five patients were younger than 5 years at diagnosis. Visual inspection and region-of-interest analysis of relative cerebral blood flow and volume on the perfusion MR images did not detect the deficits. However, this type of processing and quantitative analysis of the

perfusion MR imaging are prone to variance within and between observers which may reduce the sensitivity in detecting differences. Furthermore, the variance in location of the deficits may make voxel-based population studies more difficult and thus require a larger sample size. Another limitation to many quantitative MR perfusion methods is the assumption that the blood-brain barrier is intact and that contrast agent is restricted to the vasculature. Methods have been recently developed to account for the possible accumulation of contrast agent within the extracellular/extravascular space as well as the vascular compartment [68]. Although SPECT deficits have not been directly correlated with WM hyperintensities, they may share an underlying vascular pathophysiology that could potentially be measured with more advanced MR approaches (e.g., pulsed or continuous ASL). These approaches would allow less-invasive longitudinal assessment of cerebral perfusion changes during antileukemia therapy.

Magnetic resonance diffusion imaging studies

Two types of MR diffusion imaging are used to evaluate patients treated for ALL, diffusion-weighted and diffusion tensor imaging (DTI). Diffusion-weighted imaging provides a subjective measure of diffusion that is extensively used to evaluate ischemic events. DTI acquires a set of diffusion images in six or more directions and uses them to fully define a diffusion tensor for each point in the image [69-71]. Once the tensors have been calculated, eigen values can be derived and used to calculate apparent diffusion coefficient (ADC), perpendicular and parallel diffusion coefficients ($D_{\perp}$, $D_{\parallel}$), and fractional anisotropy (FA) maps for the whole brain, as demonstrated for a representative section in Fig. 7. The ADC measures the average diffusion distance in a region that reflects the extracellular/intracellular volume ratio and is extremely sensitive to acute ischemia. The $D_{\parallel}$ measure reflects the relative diffusion distance for water along the fiber tract. The FA and $D_{\perp}$ measures quantify the directional organization of a region and reflect the myelin integrity. These parametric maps can be analyzed using publicly available software packages such as SPM.

Diffusion-weighted studies were first used clinically to evaluate acute neurotoxicity in patients being treated with IT-MTX for ALL. Zierysen et al. [72] showed that at the end of therapy in 90 patients treated with MTX for ALL or non-B malignant non-Hodgkin lymphoma, 15 (17%) had T2 hyperintensities of whom 6 were symptomatic for acute LE, and 9 were asymptomatic. Interestingly, the spatial distribution of the hyperintensities differed in the two groups: asymptomatic subjects had localized, deep periventricular WM changes, and symptomatic subjects had hyperintensities in the supratentorial cortex, cerebellar cortex, cortical and subcortical WM, and thalamus. Unfortunately, diffusion-weighted imaging was available in only one subject who demonstrated restricted diffusion in the area of T2 hyperintensity. The neurologic symptoms resolved in 1 to 10 days, but the imaging abnormalities resolved gradually over 7 months. Maeda et al. [73] have reported case studies showing abnormal WM intensities as much as 3 years after the onset of neurologic symptoms.

Acute MTX neurotoxicity during treatment for ALL has been reported in several studies ranging from single case reports [74,75] to small studies of four to six subjects [76-78]. The combined findings from these studies form a compelling consensus that associates IT-MTX with acute neurotoxicity, which arises 6 to 11 days after treatment. The symptoms are concurrent with restricted diffusion on MR diffusion imaging and usually resolve in 1 to 7 days without intervention. T2-weighted and FLAIR imaging are often normal at onset, but hyperintensities appear later, often at or near the site of the restricted diffusion. However, the T2 hyperintensities do not always conform to the same WM that demonstrated the restricted diffusion [76]. MR diffusion imaging returns to normal shortly after the neurologic symptoms resolve but may later demonstrate increased diffusion at the site of the T2 hyperintensities as demonstrated in the patient shown in Fig. 8. Because the restricted diffusion lesions often

exceed the confines of adjacent vascular territories, this pattern of acute neurotoxicity may reflect cytotoxic edema, suggesting a reversible metabolic derangement rather than ischemia [78]. Although neurologic symptoms have been consistently associated with restricted diffusion, not all patients in every study have demonstrated imaging changes. In one study, 13 of 28 subjects who underwent MR imaging at or immediately after a neurologic event showed normal MR imaging, including diffusion-weighted imaging [77]. Unfortunately, the exact timing between onset of symptoms and MR imaging changes is not known, and these patients may have demonstrated changes later.

The use of DTI in asymptomatic patients during or after treatment for ALL is a more recent development. Khong et al. [79] prospectively tested the association of FA and intelligence quotient (IQ) in 18 ALL survivors and age-matched healthy controls. Among the ALL survivors, nine received MTX and nine underwent cranial irradiation. The FA in the WM of ALL survivors was often lower than that in the age-matched controls, and the differential between the FA in patients relative to that in controls was directly proportional to the full-scale, performance, and verbal IQ scores of the survivors. These preliminary findings suggest that WM FA is a clinically useful biomarker for the assessment of treatment-related aberrant brain maturation.

The advent of more refined DTI techniques at higher field strengths has provided a unique opportunity to more carefully examine the impact of therapy for ALL on the normal developing brain. SPM and histogram analysis [80] have been used in clinical applications to provide more sensitive global measures of change in WM integrity [79]. Newer methods such as the Reproducible Objective Quantification Scheme (ROQS) [81] focus on specific WM structures that can be used to investigate those structures most often affected by antileukemia therapy.

Neurocognitive impact of antileukemia therapy

Historically, the association between LE and neurocognitive deficits has been a matter of controversy. Measurements of LE usually consisted of detection and sometimes subjective grading of the extent. The developing brain may be more susceptible to damage because newly synthesized myelin has higher metabolic activity and lower stability, which makes it more vulnerable to the toxic effects of therapy [23]. The location, extent, and intensity of LE may have a direct impact on the maturation of WM in specific regions. Disruption of the normal maturation of WM by even transient LE may result in lower volumes of WM with decreased integrity of the myelin compared to age-matched healthy peers. Cognitive deficits may be related to the total volume of WM, and region-specific thresholds may need to be surpassed before deficits become evident [82].

Both IV-MTX and IT-MTX are associated with demyelination, loss of oligodendroglia, and atrophy of the deep cerebral WM. Rollins et al. [76] reported that acute neurotoxicity was closely associated with IT-MTX treatment in five subjects. However, Kishi et al. [83] failed to show an association between IV-MTX and acute neurologic toxicity. Both of these findings are consistent with our own experience in which acute neurologic toxicity is most often associated with IT-MTX, and chronic neurotoxicity such as decreased cognitive functioning is more likely associated with IV-MTX and LE. Montour-Proulx et al. [84] found that children treated with chemotherapy alone on the POG9605 protocol experienced substantial adverse effects on intelligence and memory functioning: 78% of 23 subjects showed LE on at least one MR image.

Subtle cognitive deficits have been observed in as many as 60% of patients with ALL and are one of the most serious long-term adverse effects associated with MTX therapy [13,25,26, 31,85,86]. Children treated for ALL with moderate-dose IV- or IT-MTX have shown declines in IQ scores comparable to those seen in children treated with low-dose cranial irradiation

[17]. Brown et al. [85] found specific attention and learning problems in children with ALL treated with chemotherapy alone. This result is consistent with the findings of Copeland et al. [86] who later showed that patients with ALL who received higher cumulative doses of IV-MTX (17 g vs. 3 g) scored significantly lower on memory-domain tests. In a study of 25 patients, Wilson et al. [25] found that 60% of the children showed neuropsychologic deficits.

The emerging consensus is that the substantial decline in IQ and academic achievement observed in childhood cancer survivors is the result of one or more cognitive-processing deficits involving attention, short-term memory, speed of processing, visuomotor coordination, or sequencing abilities [16,87-90]. Some of the most convincing evidence for these specific deficits has come from the work of Brouwers et al. [16,91], who conducted two studies using both neuropsychologic testing and CT or MR neuroimaging to evaluate long-term survivors of childhood ALL treated with chemotherapy and cranial irradiation. When combined, the data from these studies demonstrated three primary results: first, problems with reaction time, shifting of attention, and sustained attention are common among childhood ALL survivors; second, children with more severe CNS lesions (i.e. intracerebral calcifications) have the greatest deficits on these tasks; and third, problems with attention are significantly correlated with problems in higher-order cognitive processes such as memory and learning tasks. These results suggest that attention problems provide the underlying basis for difficulties with more complex cognitive tasks and academic achievement.

Hertzberg et al. [22] from the German Late Effects Group reported similar findings from a much larger sample of ALL survivors. They showed that children surviving ALL achieved low scores on the Freedom from Distractibility Factor on the Wechsler Scales and demonstrated low abilities in arithmetic computation and mental concentration. All of these deficits were correlated with imaging abnormalities. Other studies of ALL survivors have found specific deficits in measures of reaction time, processing speed, attention, concentration, and memory that cannot be explained solely on the basis of generally lowered intellectual ability [88,92, 93]. The attention ability most affected in survivors of ALL appears to be sustained attention, which is defined as the ability to maintain a consistent state of behavioral vigilance and persistence for an extended period.

Nathan et al. [94] studied neurocognitive function in ALL survivors who were not treated with cranial irradiation and demonstrated that very high-dose MTX does not have the same long-term affect on intelligence that is often associated with cranial irradiation. These findings were verified in a recent longitudinal, prospective, sibling-controlled study by Jansen et al. [95] which found no significant decline in intelligence during therapy but did observe a small relative decline in performance IQ in young children. While elimination of cranial irradiation has led to a reduction in neuropsychologic sequelae, age- and sex-related differences still exist as demonstrated by von der Weid et al. [96]. One of the most extensive studies of long-term neurocognitive outcomes in children whose treatment for ALL did not include cranial irradiation was recently conducted by Spiegler et al. [97]. They reported that survivors scored near the population mean on 17 of 18 measures of intelligence, academic achievement, attention, and memory. No differences were detected on any neurocognitive measure between patients treated on different doses of MTX. This study was discussed in the context of the reports by Buizer et al. [98,99] who identified subtle deficits in attention and visuomotor control in ALL survivors who received higher doses of IV-MTX. ALL survivors also have more behavioral and educational problems [100]. One possible explanation for a lack of difference in neurocognitive function between patients treated with different doses of MTX is differences in the dosages of leucovorin rescue, i.e. patients who received higher IV-MTX also received higher initial leucovorin doses. However, other results have suggested that high doses of leucovorin increase the risk of relapse [101].

The association between MR-diagnosed LE and cognitive deficits is not well established. Wilson et al. [25] subjectively graded MR images and detected transient WM abnormalities in 16 of 25 (65%) patients during consolidation therapy. These researchers defined psychological deficits as “any score more than one standard deviation below the population mean”. This type of cross-sectional analysis ignores the patients’ neurocognitive performance before therapy. However, although LE and neuropsychological deficits were more prevalent in patients younger than 5 years, no correlation was detected between the imaging findings and the neuropsychological findings. Additional small studies by Bakke et al. [26] and Kingma et al. [24] were also unable to detect a correlation between MR abnormalities and neuropsychological deficits. Both of these studies used subjective scoring of the MR examinations and cross-sectional analysis of the patients with respect to the normal population regardless of initial performance before therapy. The inability of these studies to detect a significant correlation may be due to small patient samples, the variance in subjective grading of the MR studies, cross-sectional analysis of neuropsychological deficits, or all three factors. Nevertheless, these results prompted a letter by Bleyer [102], in which he cautioned researchers not to overestimate the clinical significance of MR findings of LE until a relationship between the MR abnormalities and neuropsychological deficits could be determined. This relationship is still under investigation with more objective quantitative measures of LE and more targeted neurocognitive testing to more sensitively assess the impact of treatment for childhood leukemia on measures of attention, working memory, and executive functioning.

Summary and future directions

We have reviewed the rationale for continued quantitative morphologic evaluation of MR imaging in patients treated for childhood ALL including a review of the pathophysiology caused by some of the most common chemotherapy agents. We have also summarized the evolution of MR imaging from subjective grading of T2 hyperintensities to more contemporary quantitative MR imaging methods such as automated CAD and tissue segmentation for volumetric studies, tissue relaxation maps, voxel-based analyses, cerebral perfusion and diffusion tensor imaging. These methods have been employed to assess the impact of therapy on the developing brain in children during and after therapy. However, most studies thus far have focused on evaluating the whole brain to characterize global changes. Studies of specific regional or neuroanatomical structures guided by voxel-based analyses should be conducted in conjunction with targeted neurocognitive testing of lower order processes such as attention, working memory, and executive functioning. Diffusion tractography combined with functional MR imaging may further elucidate cortical regions impacted by changes in specific WM tracts. Correlating these advanced imaging measures with therapy, genetic factors [103], and sensitive neurocognitive testing of specific domains holds great potential for understanding the impact therapy on individual patients and thus facilitating the design and evaluation of behavioral or pharmacological interventions when needed.

Acknowledgements

This work was supported in part by R01-CA90246 and by Cancer Center Support (CORE) grant P30-CA21765 from the National Cancer Institute and by the American Lebanese Syrian Associated Charities (ALSAC).

References

1. Pui C-H, Evans WE. Treatment of acute lymphoblastic leukemia. *N Engl J Med* 2006;354:166–178. [PubMed: 16407512]
2. Shuper A, Stark B, Kornreich L, Cohen IJ, Avrahami G, Yaniv I. Methotrexate-related neurotoxicity in the treatment of childhood acute lymphoblastic leukemia. *Isr Med Assoc J* 2002;4:1050–1053. [PubMed: 12489505]

3. Balsom WR, Bleyer WA, Robison LL, Heyn RM, Meadows AT. Intellectual function in long-term survivors of childhood acute lymphoblastic leukemia: protective effects of pre-irradiation methotrexate? A Children's Cancer Study Group study. *Med Pediatr Oncol* 1991;19:486–492. [PubMed: 1961135]
4. Asato R, Akiyama Y, Ito M, Kubota M, Okumura R, Miki Y, Konishi J, Mikawa H. Nuclear magnetic resonance abnormalities of the cerebral white matter in children with acute lymphoblastic leukemia and malignant lymphoma during and after central nervous system prophylactic treatment with intrathecal methotrexate. *Cancer* 1992;70:1997–2004. [PubMed: 1525778]
5. Refsum H, Wesenberg F, Ueland PM. Plasma homocysteine in children with acute lymphoblastic leukemia: changes during a chemotherapeutic regimen including methotrexate. *Cancer Res* 1991;51:828–835. [PubMed: 1988122]
6. Morita H, Taguchi J, Kurihara H, Kitaoka M, Kaneda H, Kurihara Y, Maemura K, Shindo T, Minamino T, Ohno M, Yamaoki K, Ogasawara K, Aizawa T, Suzuki S, Yazaki Y. Genetic polymorphism of 5,10-methylenetetrahydrofolate reductase (MTHFR) as a risk factor for coronary artery disease. *Circulation* 1997;95:2032–2036. [PubMed: 9133512]
7. Quinn CT, Griener JC, Bottiglieri T, Hyland K, Farrow A, Kamen BA. Elevation of homocysteine and excitatory amino acid neurotransmitters in the CSF of children who receive methotrexate for the treatment of cancer. *J Clin Oncol* 1997;15:2800–2806. [PubMed: 9256122]
8. Connor JR, Menzies SL. Relationship of iron to oligodendrocytes and myelination. *Glia* 1996;17:83–93. [PubMed: 8776576]
9. Vymazal J, Brooks RA, Baumgarner C. The relation between brain iron and NMR relaxation times: an in vitro study. *Magn Reson Med* 1996;35:56–61. [PubMed: 8771022]
10. Smith B. Brain damage after intrathecal methotrexate. *J Neurol Neurosurg Psychiatry* 1975;38:810–815. [PubMed: 1058923]
11. van der Knaap, MS.; Valk, J. Magnetic resonance of myelin, myelination and myelin disorders. Springer Verlag; Heidelberg, Germany: 1995. p. 10-11.
12. Plotkin SR, Wen PY. Neurologic complications of cancer therapy. *Neurol Clin N Am* 2003;21:279–318.
13. McIntosh S, Fischer DB, Rothman SG, Rosenfield N, Lobel JS, O'Brien RT. Intracranial calcifications in childhood leukemia. *J Pediatr* 1977;91:909–913. [PubMed: 925819]
14. Peylan-Ramu N, Poplack DG, Pizzo PA, Adornato BT, Di Chiro G. Abnormal CT scans of the brain in asymptomatic children with acute lymphocytic leukemia after prophylactic treatment of the central nervous system with radiation and intrathecal chemotherapy. *N Engl J Med* 1978;298:815–818. [PubMed: 273143]
15. Ochs JJ, Parvey LS, Whitaker JN, Bowman WP, Ch'ien L, Campbell M, Coburn T. Serial cranial computed-tomography scans in children with leukemia given two different forms of central nervous system therapy. *J Clin Oncol* 1983;1:793–798. [PubMed: 6199470]
16. Brouwers P, Poplack DG. Memory and learning sequelae in long-term survivors of acute lymphoblastic leukemia: association with attention deficits. *Am J Pediatr Hematol Oncol* 1990;12:174–181. [PubMed: 2116096]
17. Ochs JJ, Mulhern RK, Fairclough D, Parvey LS, Whitaker JN, Ch'ien L, Mauer A, Simone JV. Comparison of neuropsychologic functioning and clinical indicators of neurotoxicity in long-term survivors of childhood leukemia given cranial radiation or parenteral methotrexate: a prospective study. *J Clin Oncol* 1991;9:145–151. [PubMed: 1985164]
18. Chu WCW, Chik KW, Chan YL, Yeung KW, Roebuck DJ, Howard RG, Li CK, Metreweli C. White matter and cerebral metabolite changes in children undergoing treatment for acute lymphoblastic leukemia: longitudinal study with MR imaging and 1H MR spectroscopy. *Radiology* 2003;229:659–669. [PubMed: 14576448]
19. Paakko E, Vainionpää L, Lanning M, Laitinen J, Pyhtinen J. White matter changes in children treated for acute lymphoblastic leukemia. *Cancer* 1992;70:2728–2733. [PubMed: 1423204]
20. Kingma A, Mooyaart EL, Kamps WA, Nieuwenhuizen P, Wilmink JT. Magnetic resonance imaging of the brain and neuropsychological evaluation in children treated for acute lymphoblastic leukemia at a young age. *Am J Pediatr Hematol Oncol* 1993;15:231–238. [PubMed: 8498647]

21. Paakko E, Vainionpaa L, Pyhtinen J, Lanning M. Minor changes on cranial MRI during treatment in children with acute lymphoblastic leukemia. *Neuroradiology* 1996;38:264–268. [PubMed: 8741199]
22. Hertzberg H, Huk WJ, Ueberall MA, Langer T, Meier W, Dopfer R, Skalej M, Lackner H, Bode U, Janssen G, Zintl F, Beck JD. CNS late effects after ALL therapy in childhood. Part 1: neuroradiological findings in long-term survivors of childhood ALL -an evaluation of the interferences between morphology and neuropsychological performance. *Med Pediatr Oncol* 1997;28:387–400. [PubMed: 9143382]
23. Paakko E, Harila-Saari A, Vanionpaa L, Himanen S, Pyhtinen J, Lanning M. White matter changes on MRI during treatment in children with acute lymphoblastic leukemia: correlation with neuropsychological findings. *Med Pediatr Oncol* 2000;35:456–461. [PubMed: 11070477]
24. Kingma A, van Dommelen RI, Mooyaart EL, Wilmink JT, Deelman BG, Kamps WA. Slight cognitive impairment and magnetic resonance imaging abnormalities but normal school levels in children treated for acute lymphoblastic leukemia with chemotherapy only. *J Pediatr* 2001;139:413–420. [PubMed: 11562622]
25. Wilson DA, Nitschke R, Bowman ME, Chaffin MJ, Sexauer CL, Prince JR. Transient white matter changes on MR images in children undergoing chemotherapy for acute lymphocytic leukemia: correlation with neuropsychologic deficiencies. *Radiology* 1991;180:205–209. [PubMed: 2052695]
26. Bakke SJ, Fossen A, Storm-Mathiesen I, Lie SO. Long-term cerebral effects of CNS chemotherapy in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol* 1993;10:267–270. [PubMed: 8217544]
27. Mahoney DH Jr, Shuster JJ, Nitschke R, Lauer SJ, Steuber CP, Winick NJ, Camitta B. Acute neurotoxicity in children with B-precursor acute lymphoid leukemia: an association with intermediate-dose intravenous methotrexate and intrathecal triple therapy-a Pediatric Oncology Group study. *J Clin Oncol* 1998;16:1712–1722. [PubMed: 9586883]
28. Ochs JJ, Pui C-H, Mason C, Bowman WP, Abromowitch M, Simone JV. Seizures in childhood lymphoblastic leukemia patients. *Lancet* 1984;2:1422–1424. [PubMed: 6151043]
29. Ochs JJ. Neurotoxicity due to central nervous system therapy for childhood leukemia. *Am J Pediatr Hematol Oncol* 1989;11:93–105. [PubMed: 2653080]
30. DiMario FJ Jr, Packer RJ. Acute mental status changes in children with systemic cancer. *Pediatrics* 1990;85:353–360. [PubMed: 2304789]
31. Rowland JH, Glidewell OJ, Sibley RF, Holland JC, Tull R, Berman A, Brecher ML, Harris M, Glicksman AS, Forman E, Jones B, Cohen ME, Duffner PK, Freeman AI. Effects of different forms of central nervous system prophylaxis on neuropsychologic function in childhood leukemia. *J Clin Oncol* 1984;2:1327–1335. [PubMed: 6595350]
32. Walker RW, Allen JC, Rosen G, Caparros B. Transient cerebral dysfunction secondary to high-dose methotrexate. *J Clin Oncol* 1986;14:1845–1850. [PubMed: 3465876]
33. Abromowitch M, Ochs JJ, Pui C-H, Kalwinsky D, Rivera GK, Fairclough D, Look AT, Hustu HO, Murphy SB, Evans WE, Dahl GV, Bowman WP. High-dose methotrexate improves clinical outcome in children with acute lymphoblastic leukemia: St Jude Total Therapy Study X. *Med Pediatr Oncol* 1988;16:297–303. [PubMed: 3054451]
34. Yim YS, Mahoney DH Jr, Oshman DG. Hemiparesis and ischemic changes of the white matter after intrathecal therapy for children with acute lymphocytic leukemia. *Cancer* 1991;67:2058–2061. [PubMed: 2004323]
35. Butler RW, Hill JM, Steiner PG, Meyers PA, Finlay JL. Neuropsychologic effects of cranial irradiation, intrathecal methotrexate, and systemic methotrexate in childhood cancer. *J Clin Oncol* 1994;12:2621–2629. [PubMed: 7989937]
36. Barkovitch AJ. Concepts of myelin and myelination in neuroradiology. *AJNR Am J Neuroradiol* 2000;21:1099–1109. [PubMed: 10871022]
37. Sandler DP, Ross JA. Epidemiology of acute leukemia in children and adults. *Semin Oncol* 1997;24:3–16. [PubMed: 9045302]
38. Glass JO, Reddick WE, Li C-S, Laningham FH, Helton KJ, Pui C-H. Computer-aided detection of therapy-induced leukoencephalopathy in pediatric acute lymphoblastic leukemia with intravenous high-dose methotrexate. *Magn Reson Imaging* 2006;24:785–791. [PubMed: 16824973]

39. Ashton EA, Takahashi C, Berg MJ, Goodman A, Totterman S, Ekholm S. Accuracy and reproducibility of manual and semiautomated quantification of MS lesions by MRI. *J Magn Reson Imaging* 2003;17:300–308. [PubMed: 12594719]
40. Fan YH, Lam WWM, Mok VCT, Huang RX, Wong KS. Variability and validity of a simple visual rating scale in grading white matter changes on magnetic resonance imaging. *J Neuroimaging* 2003;13:255–258. [PubMed: 12889173]
41. Parodi RC, Sardanelli F, Renzetti P, Rosso E, Losacco C, Ferrari A, Levrero F, Pilot A, Inglese M, Mancardi GL. Growing region segmentation software (GRES) for quantitative magnetic resonance imaging of multiple sclerosis: intra- and inter-observer agreement variability: a comparison with manual contouring method. *Eur Radiol* 2002;12:866–871. [PubMed: 11960240]
42. Wei X, Warfield S, Zou KH, Wu Y, Li X, Guimond A, Mugler IJP, Benson RR, Wolfson L, Weiner HL, Guttman CRG. Quantitative analysis of MRI signal abnormalities of brain white matter with high reproducibility and accuracy. *J Magn Reson Imaging* 2002;15:203–209. [PubMed: 11836778]
43. Payne ME, Fetzter DL, MacFall JR, Provenzale JM, Byrum CE, Krishnan KR. Development of a semi-automated method for quantification of MRI gray and white matter lesions in geriatric subjects. *Psychiatry Res* 2002;115:63–77. [PubMed: 12165368]
44. Swartz RH, Black SE, Feinstein A, Rockel C, Sela G, Gao FQ, Caldwell CB, Bronskill MJ. Utility of simultaneous brain, CSF and hyperintensity quantification in dementia. *Psychiatry Res* 2002;116:83–93. [PubMed: 12426036]
45. Glass JO, Reddick WE, Reeves C, Pui CH. Improving the segmentation of therapy-induced leukoencephalopathy in children with acute lymphoblastic leukemia using a priori information and a gradient magnitude threshold. *Magn Reson Med* 2004;52:1336–1341. [PubMed: 15562471]
46. Reddick WE, Glass JO, Langston JW, Helton KJ. Quantitative MRI assessment of leukoencephalopathy. *Magn Reson Med* 2002;47:912–920. [PubMed: 11979570]
47. Wilke M, Schmithorst VJ, Holland SK. Normative pediatric brain data for spatial normalization and segmentation differs from standard adult data. *Magn Reson Med* 2003;50:749–757. [PubMed: 14523961]
48. Rueckert D, Frangi AF, Schnabel JA. Automatic construction of 3-D statistical deformation models of the brain using nonrigid registration. *IEEE Trans Med Imaging* 2003;22:1014–1025. [PubMed: 12906255]
49. Wahba G. Spline models for observational data. *J R Stat Soc Ser B* 1990;10:133–150.
50. Zhang, Y.; Zuo, P.; Mulhern, RK.; Butler, RJ.; Ogg, RJ. Structural abnormalities in posterior fossa brain tumor survivors: a voxel-based morphometry study based on free-form deformation; International Society of Magnetic Resonance in Medicine, 14th Scientific Meeting; Seattle, WA. 2006; 2006.
51. Reddick WE, Glass JO, Helton KJ, Langston JW, Xiong X, Pui C-H. Leukoencephalopathy prevalence in children treated for acute lymphoblastic leukemia with high-dose methotrexate. *AJNR Am J Neuroradiol* 2005;2615:1263–1269. [PubMed: 15891195]
52. Reddick WE, Glass JO, Helton KJ, Langston JW, Chin-Shang L, Pui C-H. A quantitative MRI assessment of leukoencephalopathy in children treated for acute lymphoblastic leukemia without irradiation. *AJNR Am J Neuroradiol* 2005;26:2371–2377. [PubMed: 16219848]
53. Ji Q, Glass JO, Reddick WE. A novel, fast entropy-minimization algorithm for bias field correction in MR images. *Magn Reson Imaging* 2007;25:259–264. [PubMed: 17275623]
54. Glass JO, Ji Q, Glas LS, Reddick WE. Prediction of total cerebral tissue volumes in normal appearing brain from subsampled segmentation volumes. *Magn Reson Imaging* 2003;21:977–982. [PubMed: 14684199]
55. Reddick WE, Glass JO, Cook EN, Elkin TD, Deaton R. Automated segmentation and classification of multispectral magnetic resonance images of brain using artificial neural networks. *IEEE Trans Med Imaging* 1997;16:911–918. [PubMed: 9533591]
56. Reddick, WE.; Johnson, DP.; Glass, JO.; Zhang, Y.; Laningham, FH.; Pui, C-H. Workshop on Frontiers in Metabolic, Molecular and Clinical MR Imaging. International Society for Magnetic Resonance in Medicine; Pocono Manor, PA: 2006. 2006. Voxel-based analysis of leukoencephalopathy in children treated for acute lymphoblastic leukemia without irradiation.

57. Mabbott DJ, Noseworthy M, Bouffet E, Laughlin S, Rockel C. White matter growth as a mechanism of cognitive development in children. *Neuroimage* 2006;33:936–946. [PubMed: 16978884]
58. Reddick WE, Shan ZY, Glass JO, Helton S, Xiong X, Wu S, Bonner MJ, Howard SC, Christensen R, Khan RB, Pui C-H, Mulhern RK. Smaller white matter volumes are associated with larger deficits in attention and learning among long-term survivors of acute lymphoblastic leukemia. *Cancer* 2006;106:941–949. [PubMed: 16411228]
59. Mennes M, Stiers P, Vandenbussche E, Vercruysse G, Uyttebroeck A, De Meyer G, Van Cool SW. Attention and information processing in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. *Pediatr Blood Cancer* 2005;44:479–486.
60. Kandel, ER.; Schwartz, JH.; Jessell, TM. *Principles of neural science*. McGraw-Hill; New York: 2000.
61. Buxton RB, Frank LR, Wong EC, Siewert B, Warach S, Edelman RR. A general kinetic model for quantitative perfusion imaging with arterial spin labeling. *Magn Reson Med* 1998;40:383–396. [PubMed: 9727941]
62. Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic resonance imaging of perfusion using spin inversion of arterial water. *Proc Natl Acad Sci U S A* 1992;89:212–216. [PubMed: 1729691]
63. Roberts DA, Detre JA, Bolinger L, Insko EK, Leigh JS. Quantitative magnetic resonance imaging of human brain perfusion at 1.5 T using steady-state inversion of arterial water. *Proc Natl Acad Sci U S A* 1994;91:33–37. [PubMed: 8278387]
64. Harila-Saari A, Ahonen A, Vainionpaa L, Paakko E, Pyhtinen J, Himanen S, Torniaainen P, Lanning BM. Brain perfusion after treatment of childhood acute lymphoblastic leukemia. *J Nucl Med* 1997;38:82–88. [PubMed: 8998157]
65. Osterlundh G, Bjure J, Lannering B, Kjellmer I, Uvebrant P, Marky I. Studies of cerebral blood flow in children with acute lymphoblastic leukemia: case reports of six children treated with methotrexate examined by single photon emission computed tomography. *J Pediatr Hematol Oncol* 1997;19:28–34. [PubMed: 9065716]
66. Vera P, Rohrllich P, Stievenart JL, Elmaleh M, Duval M, Bonnin F, Bok B, Vilmer E. Contribution of single-photon emission computed tomography in the diagnosis and follow-up of CNS toxicity of a cytarabine-containing regimen in pediatric leukemia. *J Clin Oncol* 1999;17:2804–2810. [PubMed: 10561356]
67. Paakko E, Lehtinen SS, Harila-Saari A, Ahonen A, Jauhiainen J, Torniaainen P, Pyhtinen J, Lanning M. Perfusion MRI and SPECT of brain after treatment for childhood acute lymphoblastic leukemia. *Med Pediatr Oncol* 2003;40:88–92. [PubMed: 12461791]
68. Lee MC, Cha S, Chang S, Nelson SJ. Partial-volume model for determining white matter and gray matter cerebral blood volume for analysis of gliomas. *J Magn Reson Imaging* 2006;23:257–266. [PubMed: 16456821]
69. Le Bihan D, Mangin JF, Poupon C, Clark CA, Pappata S, Molko N, Chabriet H. Diffusion tensor imaging: concepts and applications. *J Magn Reson Imaging* 2001;13:534–546. [PubMed: 11276097]
70. Bassar PJ, Jones DK. Diffusion-tensor MRI: theory, experimental design and data analysis - a technical review. *NMR Biomed* 2002;15:456–467. [PubMed: 12489095]
71. Koay CG, Chang L-C, Carew JD, Pierpaoli C, Bassar PJ. A unifying theoretical and algorithmic framework for least squares methods of estimation in diffusion tensor imaging. *J Magn Reson Imaging* 2006;182:115–125.
72. Ziereisen F, Dan B, Azzi N, Ferster A, Damry N, Christophe C. Reversible acute methotrexate leukoencephalopathy: atypical brain MR imaging features. *Pediatr Radiol* 2006;36:205–212. [PubMed: 16369780]
73. Maeda M, Hayakawa J, Ueda T, Migita M, Asano T, Fukunaga Y, Amano Y. Brain white matter changes during treatment of a child for acute lymphoblastic leukemia. *J Nippon Med Sch* 2005;72:252–253. [PubMed: 16247223]
74. Sandoval C, Kutscher M, Jayabose S, Tenner M. Neurotoxicity of intrathecal methotrexate: MR imaging findings. *AJNR Am J Neuroradiol* 2003;24:1887–1890. [PubMed: 14561622]
75. Kuker W, Bader P, Herrlinger U, Heckl S, Nagele T. Transient encephalopathy after intrathecal methotrexate chemotherapy: diffusion-weighted MRI. *J Neurooncol* 2005;73:47–49. [PubMed: 15933817]

76. Rollins N, Winick N, Bash R, Booth T. Acute methotrexate neurotoxicity: findings on diffusion-weighted imaging and correlation with clinical outcome. *AJNR Am J Neuroradiol* 2004;25:1688–1695. [PubMed: 15569732]
77. Fisher MJ, Khademan ZP, Simon EM, Zimmerman RA, Bilaniuk LT. Diffusion-weighted MR imaging of early methotrexate-related neurotoxicity in children. *AJNR Am J Neuroradiol* 2005;26:1686–1689. [PubMed: 16091514]
78. Haykin ME, Gorman M, van Hoff J, Fulbright RK, Bachring JM. Diffusion-weighted MRI correlates of subacute metho-trexate-related neurotoxicity. *J Neurooncol* 2006;76:153–157.
79. Khong P-L, Leung LHT, Fung ASM, Fong DYT, Qiu D, Kwong DLW, Ooi G-C, McAlanon G, Cao G, Chan GCF. White matter anisotropy in post-treatment childhood cancer survivors: preliminary evidence of association with neurocognitive function. *J Clin Oncol* 2006;24:884–890. [PubMed: 16484697]
80. Leung LHT, Ooi G-C, Kwong DLW, Chan GCF, Cao G, Khong P-L. White-matter diffusion anisotropy after chemoirradiation: a statistical parametric mapping study and histogram analysis. *Neuroimage* 2004;21:261–268. [PubMed: 14741664]
81. Niogi SN, Mukherjee P, McCandliss BD. Diffusion tensor imaging segmentation of white matter structures using a reproducible objective quantification scheme (ROQS). *Neuroimage* 2007;35:166–174. [PubMed: 17208014]
82. Desmond DM. Cognition and white matter lesions. *Cerebrovasc Dis* 2002;13:53–57. [PubMed: 11901244]
83. Kishi S, Griener JC, Cheng C, Das S, Cook EH, Pei D, Hudson MM, Rubnitz JE, Sandlund JT, Pui C-H, Relling MV. Homocysteine, pharmacogenetics, and neurotoxicity in children with leukemia. *J Clin Oncol* 2003;21:3084–3091. [PubMed: 12915598]
84. Montour-Proulx I, Kuehn SM, Keene DL, Barrowman NJ, Hsu E, Matzinger M-A, Dunlap H, Halton JM. Cognitive changes in children treated for acute lymphoblastic leukemia with chemotherapy only according to the Pediatric Oncology Group 9605 protocol. *J Child Neurol* 2005;20:129–133. [PubMed: 15794179]
85. Brown RT, Madan-Swain A, Pais R, Lambert RG, Sexson S, Ragab A. Chemotherapy for acute lymphocytic leukemia: cognitive and academic sequelae. *J Pediatr* 1992;121:885–889. [PubMed: 1447650]
86. Copeland DR, Moore BD III, Francis DJ, Jaffe N, Culbert SJ. Neuropsychologic effects of chemotherapy on children with cancer: a longitudinal study. *J Clin Oncol* 1996;14:2826–2835. [PubMed: 8874345]
87. Copeland DR, Fletcher JM, Pfefferbaum-Levine B, Jaffe N, Ried H, Maor M. Neuropsychological sequelae of childhood cancer in long-term survivors. *Pediatrics* 1985;75:745–753. [PubMed: 3838584]
88. Goff JR, Anderson HRJ, Cooper PF. Distractibility and memory deficits in long-term survivors of acute lymphoblastic leukemia. *J Dev Behav Pediatr* 1980;1:158–163. [PubMed: 6941969]
89. Cousens P, Ungerer JA, Crawford JA, Stevens MM. Cognitive effects of childhood leukemia therapy: a case for four specific deficits. *J Pediatr Psychol* 1991;16:475–488. [PubMed: 1941427]
90. Mulhern RK, Wasserman AL, Fairclough D, Ochs J. Memory function in disease-free survivors of childhood acute lymphocytic leukemia given CNS prophylaxis with or without 1,800 cGy cranial irradiation. *J Clin Oncol* 1988;6:315–320. [PubMed: 3422262]
91. Brouwers P, Riccardi R, Fedio P, Poplack DG. Long-term neuropsychologic sequelae of childhood leukemia: correlation with CT brain scan abnormalities. *J Pediatr* 1985;106:723–728. [PubMed: 3858492]
92. Mulhern RK, Kovnar E, Langston JW, Carter M, Fairclough D, Leigh L, Kun LE. Long-term survivors of leukemia treated in infancy: factors associated with neuropsychologic status. *J Clin Oncol* 1992;10:1095–1102. [PubMed: 1318952]
93. Meadows AT, Evans AE. Effects of chemotherapy on the central nervous system. A study of parenteral methotrexate in long-term survivors of leukemia and lymphoma in childhood. *Cancer* 1976;37:1079–1085. [PubMed: 766954]
94. Nathan PC, Whitcomb T, Wolters PL, Steinberg SM, Balis FM, Brouwers P, Hunsberger S, Feusner J, Sather HN, Miser J, Odom LF, Poplack DG, Reaman GH, Bleyer WA. Very highdose methotrexate

(33.6 g/m²) as central nervous system preventive therapy for childhood acute lymphoblastic leukemia: results of National Cancer Institute/Children's Cancer Group trials CCG-191P, CCG134P and CCG144-P. *Leuk Lymphoma* 2006;47:2488–2504. [PubMed: 17169794]

95. Jansen NC, Kingma A, Schuitema A, Bouma A, Huisman J, Veerman AJP, Kamps WA. Post-treatment intellectual functioning in children treated for acute lymphoblastic leukaemia (ALL) with chemotherapy-only: a prospective, sibling-controlled study. *Eur J Cancer* 2006;42:2765–2772. [PubMed: 16935489]
96. von der Weid N, Mosimann I, Hirt A, Wacker P, Beck MN, Imbach P, Caflisch U, Niggli F, Feldges A, Wagner HP. Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: age- and sex-related differences. *Cancer* 2003;39:359–365.
97. Spiegler BJ, Kennedy K, Maze R, Greenberg ML, Weitzman S, Hitzler JK, Nathan PC. Comparison of long-term neurocognitive outcomes in young children with acute lymphoblastic leukemia treated with cranial radiation or high-dose or very high-dose intravenous methotrexate. *J Clin Oncol* 2006;24:3858–3864. [PubMed: 16921038]
98. Buizer AI, De Sonnevile LM, van den Heuvel-Eibrink MM, Njikiktjen C, Veerman AJ. Visuomotor control in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. *J Int Neuropsychol Soc* 2005;11:554–565. [PubMed: 16212682]
99. Buizer AI, De Sonnevile LM, van den Heuvel-Eibrink MM, Veerman AJ. Chemotherapy and attentional dysfunction in survivors of childhood acute lymphoblastic leukemia: effect of treatment intensity. *Pediatr Blood Cancer* 2005;45:281–290. [PubMed: 15806539]
100. Buizer AI, De Sonnevile LM, van den Heuvel-Eibrink MM, Veerman AJ. Behavioral and educational limitations after chemotherapy for childhood acute lymphoblastic leukemia or Wilms tumor. *Cancer* 2006;106:2067–2075. [PubMed: 16568441]
101. Skärby TV, Anderson H, Heldrup J, Kanerva JA, Seidel H, Schmiegelow K, Nordic Society of Paediatric Haematology and Oncology (NOPHO). High leucovorin doses during highdose methotrexate treatment may reduce the cure rate in childhood acute lymphoblastic leukemia. *Leukemia* 2006;20:1955–1962. [PubMed: 16990760]
102. Bleyer WA. Leukoencephalopathy detectable by magnetic resonance imaging: much ado about nothing? *Int J Radiat Oncol Biol Phys* 1995;32:1251–1252. [PubMed: 7607949] Regarding Matsumoto et al., *IJROBP* 32:913-918; 1995
103. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Cancer* 2007;7:192–201. [PubMed: 17318212]

Fig. 1. Transverse images from a patient after completion of consolidation therapy for ALL are shown. Images from left to right are T1-weighted, T2-weighted, PD-weighted, and FLAIR. T2 hyperintensities are clearly evident throughout the periventricular and deep white matter

Fig. 2.

A single transverse section from a FLAIR imaging set is shown on the left. The middle image is a quantitative T2 relaxation map of the same section. The corresponding quantitative T1 relaxation map is shown on the right. T2 relaxation rates in the T2 hyperintense regions are 20-60% longer than the surrounding normal-appearing white matter. The regions of greatest T2 relaxation change demonstrate T1 relaxation rates which are 25% longer than the surrounding normal-appearing white matter. Other regions of T2 hyperintensity which are clearly visible on the T2 relaxation map are indistinguishable from normal-appearing white matter on the T1 relaxation map

Fig. 3.

T2-weighted and FLAIR images from a patient after completion of consolidation therapy for ALL are shown on the left and middle, respectively. The corresponding tissue volume map is shown on the right with the T2 hyperintense regions segmented orange to contrast with the normal-appearing white matter shown in green

Fig. 4. Coregistered combination of conventional imaging, tissue volume maps, and quantitative relaxation maps of the same section. The T2 hyperintense regions are visualized on the conventional FLAIR image (a) while those regions are shown in orange on the segmented tissue volume map (b). The relaxation maps of T2 (c) and T1 (d) demonstrate the relative increase in relaxation times for these same regions

Fig. 5. Sagittal, coronal, and transverse images of patients aged less than 5 years (*left*) who demonstrated LE on second examination ($P < 0.001$), and patients aged 5 years and more (*right*) who demonstrated LE on second examination ($P < 0.05$). The *color bar* indicates F-values from statistical analysis with a cluster threshold of 100. Overlay is on the average T2 custom template

Fig. 6.

A segmented tissue map from a normal-appearing examination from a patient with sickle cell disease is shown on the left. The image on the right is a quantitative arterial spin labeling map of cerebral blood flow at this same level. This technique assesses blood flow without the use of contrast medium and could potentially be advantageous for evaluation of patients treated for ALL

Fig. 7.

A transverse FLAIR image is shown with T2 hyperintensities (a). The fractional anisotropy or FA map (b) demonstrates decreased anisotropy in the hyperintense regions. The genu and splenium of the corpus callosum and the internal capsule show high levels of anisotropy as would be expected for these regions of highly directional fiber tracts. The apparent diffusion coefficient or ADC map (c), perpendicular diffusion or $D_{\perp}$ map (d), and the parallel diffusion or $D_{\parallel}$ map (e) all demonstrate increased diffusion in the regions of hyperintensity.

Fig. 8.

T2-weighted (*top row*) and diffusion-weighted (*bottom row* when available) images from a longitudinal imaging examination in a patient who presented with right-sided weakness 7 days post IT-MTX. The T2-weighted image is normal (**a**) and the patient was scheduled for a repeat examination including diffusion-weighted imaging 4 days later. Areas of well-defined focal T2 hyperintensities are seen in the centrum semiovale (**b**) with corresponding areas of restricted diffusion (**e**). Symptoms resolved in 2 weeks with no intervention, and imaging was repeated. The previous areas of T2 hyperintensities are now larger and more diffuse (**c**), and the area of restricted diffusion now demonstrates slightly increased diffusion (**f**). Imaging obtained 7 months later show a marked decrease in the extent and intensity of the T2 hyperintensities (**d**)